Thyroid and Parathyroid

Rapid Review for BOARD Exam

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Thyroid

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Benign Thyroid Disease

Anatomy, Physiology, Pathophysiology & Ultrasonography

Anatomy of the Thyroid Gland

The thyroid is a bilobed endocrine organ located anterolaterally in the neck, spanning C5–T1. It is enveloped by the pretracheal fascia and lies anterior to the trachea.

Key anatomic relationships

- **Recurrent laryngeal nerves (RLN)** run in the tracheoesophageal groove.
- **External branch of the superior laryngeal nerve (EBSLN)** runs near the superior thyroid vessels.
- **Parathyroid glands** lie on the posterior surface of the thyroid.
- **Berry's ligament** anchors the gland to the trachea.

Blood supply

- **Superior thyroid artery** (ECA branch).
- **Inferior thyroid artery** (thyrocervical trunk).
- Venous drainage via superior, middle, and inferior thyroid veins.

Lymphatic drainage

- Central compartment (Level VI).
- Lateral neck (Levels II–V).

Thyroid Cellular Physiology

The thyroid follicle is the functional unit.

Key steps in hormone synthesis

- **Iodide uptake** via NIS on basolateral membrane.
- **Iodide transport** into colloid via pendrin.
- **Organification** by TPO → MIT/DIT formation.
- **Coupling** by TPO → T4 (DIT+DIT), T3 (MIT+DIT).
- **Storage** in colloid bound to thyroglobulin.
- **Release** via endocytosis and lysosomal proteolysis.
- **Transport** into circulation via MCT8.

"The crucial first step… is the active transport of iodine into the thyroid follicular cells… mediated by the Na/I symporter."

Thyroid hormone transport

- 0.03% of T4 and 0.3% of T3 are free.
- Binding proteins:
  - **TBG** (75% of T4/T3)
  - **Transthyretin**
  - **Albumin**

Deiodinases

- DIO1/2 → activate T4 → T3.
- DIO3 → inactivates T4/T3.

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Hypothalamic–Pituitary–Thyroid Axis

- TRH → stimulates TSH.
- TSH → stimulates thyroid hormone synthesis.
- T4/T3 → negative feedback.
- TSH secretion is **pulsatile** and affected by glucocorticoids, dopamine, somatostatin, retinoids.

"TSH secretion is pulsatile… and is affected by glucocorticoids, retinoids, somatostatin, and dopamine."

Ultrasonography

Ultrasound is the first-line imaging modality.

Advantages

- High-resolution detail.
- Real-time assessment of tissue mobility.
- Excellent for cervical lymph nodes.

Limitations

- Poor for substernal extension.
- Operator dependent.

US features of malignancy

- Hypoechoic
- Irregular margins
- Microcalcifications
- Taller-than-wide
- Intranodular vascularity

Non-Toxic Thyroid Nodules & Multinodular Goiter

Epidemiology

- Very common; prevalence increases with age.
- More common in iodine-deficient regions.
- Most nodules are benign.

Etiology

- Iodine deficiency
- Genetic predisposition
- Somatic mutations (TSHR, RAS)
- Growth factors (TSH, IGF-1)
- Autoimmune thyroiditis

Evaluation of Thyroid Nodules

Step 1: TSH

- Low TSH → consider radionuclide scan (hyperfunctioning nodule).
- Normal/high TSH → proceed to ultrasound.

Step 2: Ultrasound

Assess:

- Echogenicity
- Margins
- Calcifications
- Shape
- Vascularity
- Cervical nodes

Step 3: FNA

Based on ATA/TI-RADS criteria.

Step 4: Molecular testing

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Useful for indeterminate nodules (Bethesda III/IV).

Multinodular Goiter (MNG)

Clinical features

- Asymptomatic enlargement
- Compressive symptoms:
  - Dyspnea
  - Dysphagia
  - Hoarseness
- Substernal extension
- Cosmetic concerns

Indications for surgery

- Suspicion of malignancy
- Compressive symptoms
- Substernal extension
- Hyperfunctioning nodules (if RAI not preferred)
- Cosmetic reasons

Complications of large goiters

- Tracheal deviation
- Tracheomalacia
- RLN stretch injury
- Venous congestion

Graves' Disease & Toxic Nodular Goiter

Graves' Disease

Pathophysiology

Autoimmune stimulation of TSH receptor by **TSH receptor antibodies (TRAb)**.

Clinical features

- Hyperthyroidism
- Diffuse goiter
- Ophthalmopathy
- Pretibial myxedema
- Thyroid bruit

Diagnosis

- Low TSH, high T3/T4
- Positive TRAb
- High uptake on RAI scan

Treatment options

- **Antithyroid drugs**
- **Radioactive iodine**
- **Surgery** (indications):
  - Large goiter
  - Compressive symptoms
  - Suspicious nodules
  - Pregnancy planning
  - Ophthalmopathy

Toxic Multinodular Goiter / Toxic Adenoma

Pathophysiology

Autonomous hormone production from nodules.

Clinical features

- Hyperthyroidism
- No ophthalmopathy
- Nodular thyroid on exam/US

Diagnosis

- Low TSH, high T3/T4
- **Patchy or focal uptake** on RAI scan

Treatment

- RAI
- Surgery
- Antithyroid drugs (temporary control)

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Thyroiditis (Hashimoto, de Quervain, Riedel)

Hashimoto Thyroiditis

Pathophysiology

Autoimmune destruction of thyroid gland.

Clinical features

- Firm, rubbery goiter
- Hypothyroidism
- High TPO antibodies
- Increased risk of thyroid lymphoma

Diagnosis

- High TSH, low free T4
- High TPO antibodies
- Heterogeneous US pattern

Subacute (de Quervain) Thyroiditis

Pathophysiology

Post-viral inflammatory process.

Clinical features

- Painful thyroid
- Hyperthyroid → hypothyroid → recovery
- Elevated ESR/CRP
- Low uptake on RAI scan

Diagnosis

- High ESR
- Low uptake
- Tender thyroid

Riedel Thyroiditis

Pathophysiology

IgG4-related fibrosing disorder.

Clinical features

- "Woody," rock-hard thyroid
- Fixed to surrounding tissues
- Mimics ATC
- Compressive symptoms

Diagnosis

- Core biopsy
- IgG4 staining
- Imaging showing invasive fibrosis

High-Yield Benign Thyroid Pearls

- NIS transports iodide; TPO mediates organification and coupling.
- TBG binds most circulating T4/T3.
- Overt hypothyroidism = high TSH + low free T4.
- Subclinical hypothyroidism = high TSH + normal free T4.
- Graves' disease → TRAb positive.
- Thyroiditis → low uptake on RAI scan.
- Hashimoto's increases risk of thyroid lymphoma.
- Toxic nodular goiter common in older adults; no ophthalmopathy.
- US malignancy signs: microcalcifications, irregular margins, taller-than-wide.
- Riedel thyroiditis mimics ATC.

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THYROID CANCER

Papillary Thyroid Carcinoma (PTC)

Epidemiology & Background

PTC is the **most common endocrine malignancy** and the most common thyroid cancer. Incidence is rising globally, largely due to increased imaging sensitivity rather than true disease increase. The document notes:

"PTC is by far the most common endocrine malignancy, and the incidence… is rapidly increasing… largely responsible [is] the increased sensitivity and application of medical imaging."

Autopsy studies show a large reservoir of occult disease:

"Autopsy series… have found rates of up to 30%."

Most patients present with small, asymptomatic nodules; 80% are female, most commonly age 45–54.

Risk Factors

Only two consistently established risk factors:

- **Childhood/adolescent ionizing radiation exposure**
  - Highest risk if exposed <5 years old
  - Risk persists for **60+ years**
  - Tumors are *not* more aggressive than non-radiation PTC

"Those exposed at younger ages… have the highest risk… persists for up to 60 years."

- **Familial non-medullary thyroid cancer**
  - Defined as ≥3 first-degree relatives with thyroid cancer

"Diagnosed when three additional first-degree relatives are also affected."

Clinical Presentation

Typical presentation:

- Female, 45–54
- Small thyroid nodule (<2 cm)
- Asymptomatic
- Moves with swallowing
- 20–30% have nodal disease at presentation
- <5% have locally invasive disease

Symptoms suggesting invasion:

- Dysphonia
- Dysphagia
- Dyspnea
- Hemorrhage
- Asphyxia (rare)

Natural History

PTC has **excellent prognosis**:

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"10-year survival… is 99%."
Key biological features:

- **Slow growth**, but **high lymphatic spread**
- Hematogenous spread is rare (contrast with FTC)
- Occult nodal metastases common (up to 30–40%)
- Distant metastases in <5% (lungs most common)

Growth varies by age:
"Those diagnosed in their 20s show advancement up to 24%… age ≥60 have growth <3%."

Diagnostic Workup
History & Physical

- Voice changes → possible RLN involvement
- Swallowing/breathing changes → invasive disease
- Family history
- Prior radiation exposure
- Voice assessment is essential pre-op

Laboratory

- TSH
- Calcitonin (in some regions)

Imaging
Ultrasound = first-line

- Most accurate for thyroid and cervical nodes
- Guides FNA
- Uses risk stratification systems (TI-RADS, ATA)

CT neck/chest with contrast
indicated for:

- Overt nodal disease
- Suspected invasive disease
- Mediastinal node evaluation

"The need for accurate presurgical information… far outweighs concerns about iodinated contrast."
FDG-PET

- Limited role
- Useful only for de-differentiated, RAI-negative disease

Biopsy

- **FNA** is standard
- **Core biopsy** used by some for more tissue
- Bethesda system used for reporting

Risk Stratification
Two parallel systems:
1. Survival Predictors

- Age (>55 worse)
- Tumor size (>4 cm worse)
- Gross extrathyroidal extension
- Distant metastases

2. Recurrence Predictors

- Multicentricity
- Lymphatic/vascular invasion
- Microscopic ETE
- Nodal disease volume
- Extranodal extension

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"Features… combined into a recurrence risk continuum promoted by the ATA."

Surgical Management

Low-Risk PTC

Criteria:

- Tumor <4 cm
- No gross ETE
- No nodal disease
- No distant metastases

Recommended operation: thyroid lobectomy

Benefits:

- Removes disease
- Preserves contralateral RLN and parathyroids
- Lower complication rates
- Less lifelong thyroid hormone dependence

"Such patients can normally be considered candidates for a thyroid lobectomy."

High-Risk PTC

Criteria:

- Tumor >4 cm
- Gross ETE
- Clinically apparent nodal disease
- Distant metastases

Recommended operation: total thyroidectomy + compartment-oriented neck dissection

Followed by **RAI**.

Nodal Management

Central Neck (Level VI)

- **Therapeutic dissection** for clinically involved nodes
- **Prophylactic dissection**:
  - Not recommended for low-risk disease
  - Recommended for **invasive primary tumors**

"In aggressive primary disease, rates of occult nodal disease are high."

Lateral Neck (Levels II–V)

- **Only for clinically/radiologically involved nodes**
- Must be **compartment-oriented**

"Level II–V neck dissection is recommended to minimize recurrent disease."

Radioactive Iodine (RAI)

Indications:

- High-risk disease
- Gross ETE
- Large tumors
- Clinically significant nodal disease
- Distant metastases

Not indicated for low-risk PTC:

"In low-risk patients, there is little to gain from RAI."

Side effects:

- Xerostomia
- Dry eyes

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- Dysphagia
- Reduced QoL

Complications of Surgery

Complication rates depend heavily on surgeon volume:

"Annual volume in the low to mid-20s is required to minimize complications."

Population-based rates:

- **Temporary hypocalcemia**: ~20%
- **Permanent hypocalcemia**: 1.8–5%
- **Vocal cord paralysis**: ~8%
- **Complication rate**:
  - Unilateral surgery: ~10%
  - Bilateral surgery: ~20%

"Even high-volume surgeons have higher complication rates in total thyroidectomy versus lobectomy."

Active Surveillance

Ideal for:

- Tumors ≤1 cm
- Rim of normal thyroid tissue
- Reliable follow-up
- No aggressive features

Outcomes:

"Only a small proportion… demonstrate progression… all patients with growth have been successfully rescued."

Being expanded to tumors <2 cm in some centers.

Follow-Up

Core components:

- Clinical exam
- Ultrasound
- Thyroglobulin (if total thyroidectomy)

Dynamic Risk Stratification

At 12 months:

- **Excellent response** → <5% recurrence
- **Indeterminate** → ~20% recurrence
- **Biochemical incomplete** → persistent Tg
- **Structural incomplete** → persistent disease

"Patients in the lowest-risk category have <5% chance of recurrence."

Follow-up interval: every 6–12 months.

Follicular Thyroid Carcinoma (FTC)

Epidemiology & Background

FTC is the **second most common differentiated thyroid cancer**, behind PTC. It is less common in iodine-sufficient regions and more common in iodine-deficient areas.

FTC tends to present in **older patients** compared with PTC and has a **higher rate of distant metastasis** at diagnosis.

Key contrasts with PTC:

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- FTC spreads **hematogenously**, not lymphatically.
- FTC is more likely to present with **distant metastases** (lung, bone).
- FTC is less likely to present with nodal disease.

Pathology & Variants

FTC is defined by **capsular and/or vascular invasion**. Cytology cannot reliably distinguish follicular adenoma from carcinoma; diagnosis requires histologic evaluation of the capsule.

Variants include:

- **Minimally invasive FTC** — capsular invasion only
- **Widely invasive FTC** — extensive capsular and vascular invasion
- **Hurthle cell carcinoma** (now considered a separate entity in many classifications)

Key board point:

Vascular invasion = higher recurrence and mortality risk.

Risk Factors

- **Iodine deficiency**
- **Radiation exposure** (less strongly associated than in PTC)
- **Older age**
- **Female sex**
- **Genetic predisposition** (rare)

Clinical Presentation

FTC typically presents as:

- A solitary thyroid nodule
- Firm, smooth, and mobile
- Less likely to have cervical lymphadenopathy
- More likely to have distant metastases at presentation (lung, bone)

Symptoms of metastatic disease:

- Bone pain
- Pathologic fractures
- Respiratory symptoms (lung mets)

Natural History

FTC has a more aggressive course than PTC but still falls under differentiated thyroid cancer with generally good prognosis when minimally invasive.

Key biological features:

- **Hematogenous spread** (lungs, bone, brain)
- **Low rate of nodal metastasis**
- **Prognosis strongly tied to degree of invasion**
- **Older age worsens prognosis**

Minimally invasive FTC behaves similarly to low-risk PTC. Widely invasive FTC behaves more aggressively and often requires multimodal therapy.

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Diagnostic Workup

Ultrasound

Findings are often nonspecific:

- Solid, hypoechoic nodule
- Smooth margins
- No microcalcifications (unlike PTC)

Ultrasound cannot distinguish adenoma vs carcinoma.

FNA Cytology

Bethesda IV ("Follicular neoplasm" or "Suspicious for follicular neoplasm")

But FNA cannot diagnose FTC because **capsular/vascular invasion cannot be assessed**.

Molecular Testing

May help risk-stratify indeterminate nodules:

- RAS mutations common
- PAX8-PPARγ rearrangements associated with FTC

Definitive Diagnosis

Requires **lobectomy** to evaluate capsular and vascular invasion.

Risk Stratification

High-risk features:

- Age >55
- Tumor >4 cm
- Vascular invasion
- Widely invasive histology
- Distant metastases
- Poorly differentiated components

Low-risk features:

- Minimally invasive
- Capsular invasion only
- Tumor <4 cm
- No vascular invasion
- No metastases

Surgical Management

Initial Operation

Thyroid lobectomy is the diagnostic and therapeutic operation for most indeterminate nodules.

If postoperative pathology shows:

- **Minimally invasive FTC without vascular invasion** → lobectomy alone is adequate.
- **Vascular invasion or widely invasive FTC** → completion thyroidectomy recommended.

Total Thyroidectomy Indications

- Tumor >4 cm
- Vascular invasion
- Widely invasive histology
- Distant metastases
- Need for RAI therapy
- Bilateral disease
- High-risk patient factors

Nodal Surgery

Unlike PTC:

- **Prophylactic central neck dissection is NOT recommended**
- **Therapeutic dissection only** for clinically involved nodes (rare)

Radioactive Iodine (RAI)

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FTC is generally **more RAI-avid** than PTC.
Indications:

- Tumor >4 cm
- Vascular invasion
- Widely invasive disease
- Distant metastases
- High-risk features

Minimally invasive FTC without vascular invasion does **not** benefit from RAI.

Distant Metastases
Most common sites:

- **Lung**
- **Bone**
- **Brain** (less common)

Bone metastases may be RAI-avid but often require multimodal therapy:

- RAI
- External beam radiation
- Bisphosphonates or denosumab
- Surgical stabilization for fractures

Prognosis
Prognosis depends heavily on:

- Age
- Tumor size
- Degree of invasion
- Vascular invasion
- Distant metastases

Minimally invasive FTC has excellent outcomes. Widely invasive FTC has significantly worse survival.

Follow-Up
Follow-up mirrors differentiated thyroid cancer protocols:

- **Thyroglobulin** monitoring (after total thyroidectomy)
- **Neck ultrasound**
- **RAI scans** for high-risk patients
- **Cross-sectional imaging** for metastatic disease

Dynamic risk stratification applies similarly to PTC.

Board-Favorite Pearls

- FTC spreads **hematogenously**, not lymphatically.
- FNA **cannot** diagnose FTC — requires capsular/vascular invasion.
- **Vascular invasion** is the strongest predictor of recurrence and mortality.
- Minimally invasive FTC → **lobectomy alone** is adequate.
- Widely invasive FTC → **total thyroidectomy + RAI**.
- Bone metastases may require multimodal therapy.
- FTC is more common in **iodine-deficient regions**.

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Hürthle Cell Carcinoma (HCC)

Overview & Background

Hürthle cell carcinoma is a distinct thyroid malignancy historically grouped with follicular thyroid carcinoma but now recognized as a **separate entity** due to its unique biology, behavior, and molecular profile.

Key characteristics:

- Composed of **oncocytic cells** (Hürthle cells) with abundant granular eosinophilic cytoplasm due to mitochondrial proliferation.
- More aggressive than classic FTC.
- Higher rates of **recurrence**, **distant metastasis**, and **RAI resistance**.
- More common in **older patients**.

Epidemiology

- Represents **3–10%** of differentiated thyroid cancers.
- More common in **women**, but less female-predominant than PTC.
- Typically presents in **older adults** (6th–7th decade).
- Incidence increases with age.

Pathology

Hürthle cell tumors are defined by:

- **Oncocytic cells** with granular eosinophilic cytoplasm.
- Large, hyperchromatic nuclei.
- Prominent nucleoli.

Diagnosis requires:

- **Capsular and/or vascular invasion** → carcinoma.
- No invasion → adenoma.

Variants:

- **Minimally invasive HCC** — capsular invasion only.
- **Widely invasive HCC** — extensive capsular and vascular invasion; highly aggressive.

Key board point:

Hürthle cell carcinoma has **higher rates of vascular invasion** than FTC.

Molecular Features

Distinct from PTC and FTC:

- **Mitochondrial DNA mutations** common.
- **RAS mutations** less common than in FTC.
- **PAX8-PPARγ** rearrangements uncommon.
- Genomic instability is more pronounced.

These molecular differences support its classification as a separate entity.

Clinical Presentation

Typical presentation:

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- Solitary thyroid nodule.
- Firm, solid, often larger at diagnosis than PTC.
- Less likely to present with nodal disease than PTC.
- More likely to present with **distant metastases** than FTC.

Symptoms of advanced disease:

- Neck mass
- Dysphagia
- Hoarseness
- Symptoms from distant metastases (bone pain, respiratory symptoms)

Natural History

HCC is more aggressive than FTC and PTC.

Key biological behaviors:

- **Higher recurrence rates**
- **Higher distant metastasis rates**
- **Lower RAI avidity**
- **Higher mortality**, especially in widely invasive disease

Most common metastatic sites:

- **Lung**
- **Bone**
- **Mediastinum**
- **Liver** (more common than in FTC)

Diagnostic Workup

Ultrasound

Findings are nonspecific:

- Solid, hypoechoic nodule
- May have irregular margins
- Often larger than PTC at presentation

FNA Cytology

Bethesda IV or V:

- "Hürthle cell neoplasm"
- "Suspicious for Hürthle cell carcinoma"

But FNA **cannot** distinguish adenoma vs carcinoma — requires histologic evaluation of invasion.

Molecular Testing

Limited utility:

- Oncocytic features reduce predictive value of common mutation panels.
- High false-positive rate for malignancy prediction.

Cross-Sectional Imaging

Indicated for:

- Large tumors
- Suspected invasion
- Suspected metastases

Risk Stratification

High-risk features:

- Age >55
- Tumor >4 cm
- Vascular invasion
- Widely invasive histology
- Distant metastases
- Poorly differentiated features

Low-risk features:

- Minimally invasive
- Capsular invasion only
- Tumor <4 cm

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- No vascular invasion

Surgical Management

Initial Operation

Thyroid lobectomy is acceptable for:

- Minimally invasive HCC
- Tumors <4 cm
- No vascular invasion
- No metastases

Total thyroidectomy recommended for:

- Tumor >4 cm
- Vascular invasion
- Widely invasive disease
- Bilateral disease
- Need for RAI therapy
- High-risk features

Nodal Surgery

- HCC has **low nodal metastasis rates**.
- **Therapeutic dissection only** for clinically involved nodes.
- **Prophylactic dissection is not recommended**.

Radioactive Iodine (RAI)

Hürthle cell carcinoma is **less RAI-avid** than FTC or PTC.

Indications:

- Widely invasive disease
- Vascular invasion
- Distant metastases
- High-risk features

However:

- Response rates are lower.
- RAI may not improve survival in many cases.

Distant Metastases

More common than in FTC:

- Lung
- Bone
- Liver
- Mediastinum

Management:

- RAI (if avid)
- External beam radiation for bone lesions
- Surgical stabilization for fractures
- Systemic therapy for progressive disease (TKIs)

Prognosis

Prognosis depends on:

- Degree of invasion
- Vascular invasion
- Tumor size
- Age
- Metastatic status

Minimally invasive HCC:

- Excellent prognosis
- Similar to minimally invasive FTC

Widely invasive HCC:

- Poor prognosis
- High recurrence and mortality rates

Follow-Up

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Follow-up mirrors differentiated thyroid cancer protocols:

- **Thyroglobulin** monitoring (after total thyroidectomy)
- **Neck ultrasound**
- **Cross-sectional imaging** for high-risk patients
- **RAI scans** if RAI was used

HCC often requires more intensive surveillance due to higher recurrence risk.

Board-Favorite Pearls

- Hürthle cell carcinoma is **more aggressive** than FTC.
- **FNA cannot diagnose HCC** — requires capsular/vascular invasion.
- **Vascular invasion** is the strongest predictor of poor outcome.
- **Less RAI-avid** than other differentiated thyroid cancers.
- **Total thyroidectomy** recommended for tumors >4 cm or with vascular invasion.
- **Distant metastases** more common than in FTC.
- **Prophylactic nodal dissection is not recommended**.

Medullary Thyroid Carcinoma (MTC)

Overview

Medullary thyroid carcinoma arises from **parafollicular C-cells** and is a **neuroendocrine tumor** that secretes **calcitonin**. It behaves very differently from differentiated thyroid cancers (PTC/FTC) and requires a completely distinct diagnostic and surgical approach.
Key defining features:

- Derived from **neural crest–derived C-cells**
- Produces **calcitonin** (tumor marker)
- Associated with **RET mutations**
- Does **not** take up radioactive iodine
- Requires **total thyroidectomy** even for small tumors
- High rate of **nodal metastasis** at presentation

Epidemiology

- Accounts for **3–5%** of all thyroid cancers.
- Occurs in **sporadic** and **hereditary** forms.
- Hereditary MTC occurs in:
  - **MEN2A**
  - **MEN2B**
  - **Familial MTC (FMTC)**

Hereditary cases account for **20–25%** of all MTC.

Genetics

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RET Proto-Oncogene

RET mutations drive nearly all hereditary MTC and a significant portion of sporadic cases.

- **MEN2A**: RET mutations in codons 609, 611, 618, 620, 634
- **MEN2B**: RET M918T (most aggressive)
- **FMTC**: RET mutations without other MEN2 features

Key board point:

All patients with MTC must undergo germline RET testing, regardless of age or family history.

Pathophysiology

- Originates from **C-cells** in the thyroid.
- Produces **calcitonin** and **CEA**.
- Often multicentric in hereditary cases.
- Early and frequent **lymph node metastasis**.
- Hematogenous spread to **liver, lung, bone** in advanced disease.

Clinical Presentation

Common presentations:

- Thyroid nodule
- Cervical lymphadenopathy
- Diarrhea (from calcitonin or VIP secretion)
- Flushing (rare)
- Symptoms of metastatic disease (bone pain, liver dysfunction)

Hereditary MTC may present earlier and is often bilateral/multifocal.

Associated Syndromes

MEN2A

- MTC (near 100% penetrance)
- Pheochromocytoma (50%)
- Primary hyperparathyroidism (20–30%)

MEN2B

- MTC (aggressive, early onset)
- Pheochromocytoma
- Mucosal neuromas
- Marfanoid habitus
- Intestinal ganglioneuromatosis

FMTC

- MTC only
- Later onset, more indolent

Diagnostic Workup

Laboratory

- **Calcitonin** (primary tumor marker)
- **CEA** (correlates with tumor burden)
- **RET germline testing** (mandatory)
- **Screen for pheochromocytoma** before surgery:

Sam Moslemi, M.D.

    - Plasma metanephrines or 24-hr urine metanephrines

Board-critical rule:

Always rule out pheochromocytoma before thyroid surgery in suspected hereditary MTC.

Imaging

- **Neck ultrasound** for thyroid and cervical nodes
- **CT/MRI** for advanced disease
- **FDG-PET** or **DOTATATE PET** for metastatic disease

Biopsy

- FNA shows neuroendocrine features
- Calcitonin washout from FNA can confirm diagnosis

Risk Stratification

Prognostic factors:

- Stage at diagnosis
- Calcitonin level
- CEA level
- Rate of calcitonin doubling time
- Presence of distant metastases
- RET mutation type (M918T = worst)

Calcitonin doubling time:

- <6 months → poor prognosis
- 2 years → favorable prognosis

Surgical Management

Primary Treatment

Total thyroidectomy + central neck dissection (level VI) is the standard of care.

Rationale:

- High rate of bilateral and multifocal disease
- Early central lymph node metastasis

Lateral Neck Dissection

Indicated when:

- Preoperative imaging shows nodal disease
- Calcitonin >200 pg/mL (high likelihood of lateral metastasis)

Extent of Surgery

- **Central neck dissection**: always performed
- **Lateral neck dissection**: therapeutic, not prophylactic
- **Re-operations**: high morbidity; avoid unless clear structural disease

Special Considerations

- If pheochromocytoma is present → **adrenalectomy first**, then thyroidectomy.
- In hereditary MTC, prophylactic thyroidectomy timing depends on RET mutation risk category.

Radioactive Iodine

Sam Moslemi, MD

MTC does **not** take up RAI.
RAI has **no role** in treatment.

Adjuvant Therapy

External Beam Radiation

Considered for:

- Unresectable disease
- Positive margins (R1/R2)
- Locally advanced disease with high recurrence risk

Systemic Therapy

Used for metastatic or progressive disease:

- **Tyrosine kinase inhibitors (TKIs)**:
  - Vandetanib
  - Cabozantinib
- **RET-specific inhibitors** (highly effective):
  - Selpercatinib
  - Pralsetinib

RET-targeted therapy is now standard for metastatic RET-mutated MTC.

Follow-Up

Tumor Markers

- **Calcitonin** (most sensitive)
- **CEA**

Monitor doubling times — powerful prognostic indicator.

Imaging

- Ultrasound for neck recurrence
- CT/MRI/PET for metastatic disease

Patterns of Recurrence

- Cervical lymph nodes
- Mediastinum
- Liver
- Lungs
- Bone

Prognosis

Survival depends heavily on:

- Stage at diagnosis
- Calcitonin/CEA doubling time
- RET mutation type
- Completeness of surgical resection

Best outcomes:

- FMTC
- Early MEN2A detection
- Small, node-negative tumors

Worst outcomes:

- MEN2B (M918T mutation)
- Advanced nodal disease
- Distant metastases

Board-Favorite Pearls

- MTC arises from **C-cells**, not follicular cells.
- Produces **calcitonin** → key diagnostic and follow-up marker.
- **RET mutation testing is mandatory** for all patients.
- Always **rule out pheochromocytoma before thyroid surgery**.
- Requires **total thyroidectomy + central neck dissection**.

Sam Moslemi, MD

- Does **not** take up RAI.
- Calcitonin **doubling time** is a major prognostic factor.
- MEN2B (M918T) is the **most aggressive** form.
- RET-targeted TKIs (selpercatinib, pralsetinib) are highly effective in metastatic disease.

Cross-Cutting Topics (Imaging, Staging, RAI, Complications, Follow-Up)

Imaging Across Thyroid Cancers

Ultrasound (US)

Ultrasound is the foundational imaging modality for thyroid cancer evaluation and follow-up. It provides high-resolution assessment of thyroid parenchyma and cervical lymph nodes.

Key capabilities:

- Characterizes thyroid nodules (echogenicity, margins, calcifications).
- Identifies suspicious lymph nodes (loss of hilum, microcalcifications, cystic change).
- Guides FNA biopsy.
- Essential for surveillance after surgery.

Risk stratification systems (e.g., ATA, TI-RADS) help determine biopsy thresholds.

CT Neck/Chest with Contrast

Indications:

- Suspected extrathyroidal extension.
- Bulky nodal disease.
- Mediastinal lymphadenopathy.
- Preoperative mapping of invasive tumors.
- Evaluation for pulmonary metastases.

Important point:

- Iodinated contrast **does not meaningfully delay RAI therapy**, and the need for accurate staging outweighs theoretical concerns.

MRI

Used when:

- CT contrast is contraindicated.
- Evaluating tracheal, esophageal, or vascular invasion.
- Assessing spinal or CNS metastases.

Nuclear Medicine

RAI Scans (I-123 or I-131)

Used for:

- Post-thyroidectomy remnant evaluation.

Sam Moslemi, M.D.

- Detecting RAI-avid metastases in differentiated thyroid cancer (PTC/FTC).

FDG-PET

Indications:

- De-differentiated thyroid cancer.
- RAI-negative metastatic disease.
- Aggressive histologic variants.

DOTATATE PET

Useful in:

- Medullary thyroid carcinoma.
- Neuroendocrine-type metastases.

Staging Systems

AJCC TNM Staging (8th Edition)

Key principles:

- Age cutoff for differentiated thyroid cancer is **55 years**.
- PTC/FTC staging heavily influenced by age.
- MTC staging does **not** use age as a factor.
- Anaplastic thyroid cancer is always **Stage IV**.

T-Stage Highlights

- **T1**: ≤2 cm, confined to thyroid.
- **T2**: 2–4 cm, confined to thyroid.
- **T3**: >4 cm or minimal extrathyroidal extension.
- **T4a**: Gross invasion into strap muscles, larynx, trachea, esophagus.
- **T4b**: Invasion into prevertebral fascia or encasing carotid artery.

N-Stage

- **N1a**: Central compartment nodes (Level VI).
- **N1b**: Lateral neck or mediastinal nodes.

M-Stage

- **M1**: Distant metastases (lung, bone, liver, brain).

Surgical Principles Across Thyroid Cancers

Thyroid Lobectomy

Indications:

- Low-risk PTC (≤4 cm, no ETE, no nodal disease).
- Minimally invasive FTC without vascular invasion.
- Diagnostic surgery for indeterminate nodules.
- Patients prioritizing lower complication risk.

Advantages:

- Lower risk of hypocalcemia.
- Lower risk of RLN injury.
- Less lifelong thyroid hormone dependence.

Total Thyroidectomy

Indications:

Sam Mosleh, MD

- High-risk PTC (tumor >4 cm, gross ETE, nodal disease).
- Widely invasive FTC or vascular invasion.
- Hürthle cell carcinoma >4 cm or invasive.
- All medullary thyroid carcinoma.
- Need for RAI therapy.
- Bilateral disease.

Risks:

- Higher RLN injury risk.
- Higher hypocalcemia risk.
- Higher overall complication rate.

Central Neck Dissection (Level VI)

Therapeutic for:

- Clinically involved nodes in PTC/FTC.
- All MTC cases.

Prophylactic:

- Not recommended for low-risk PTC.
- Recommended for invasive primary tumors.
- Not recommended for FTC or HCC.

Lateral Neck Dissection (Levels II–V)

Indications:

- Radiologically or clinically involved nodes.
- MTC with calcitonin >200 pg/mL or imaging-proven metastases.

Must be **compartment-oriented**, not "berry picking."

Radioactive Iodine (RAI) Therapy Indications

PTC/FTC:

- Tumor >4 cm.
- Gross extrathyroidal extension.
- Clinically significant nodal disease.
- Distant metastases.
- High-risk histologic variants.

Not indicated for:

- Low-risk PTC.
- Minimally invasive FTC without vascular invasion.
- Hürthle cell carcinoma (often RAI-resistant).
- Medullary thyroid carcinoma (no iodine uptake).

Mechanism

RAI ablates:

- Thyroid remnant tissue.
- RAI-avid metastatic disease.

Requires:

- TSH stimulation (thyroid hormone withdrawal or rhTSH).
- Low-iodine diet.

Side Effects

Sam Mosleni, MD.

- Xerostomia.
- Dry eyes.
- Dysphagia.
- Altered taste.
- Sialadenitis.
- Rare: secondary malignancies.

Complications of Thyroid Surgery
Recurrent Laryngeal Nerve (RLN) Injury

- Temporary: hoarseness, weak voice.
- Permanent: breathy voice, aspiration risk.
- Bilateral injury → airway compromise → tracheostomy.

Risk higher in:

- Total thyroidectomy.
- Re-operations.
- Invasive tumors.

Superior Laryngeal Nerve Injury

- Loss of high-pitch voice.
- Reduced vocal stamina.
- Particularly impactful for professional voice users.

Hypocalcemia / Hypoparathyroidism

- Temporary hypocalcemia: ~20% after total thyroidectomy.
- Permanent hypoparathyroidism: 1.8–5%.

Symptoms:

- Perioral numbness.
- Tetany.
- Muscle cramps.
- Cognitive fog.

Bleeding / Hematoma

- Life-threatening airway compromise.
- Requires immediate bedside decompression.

Infection

- Rare due to excellent vascularity.

Follow-Up Principles Across Thyroid Cancers
Differentiated Thyroid Cancer (PTC/FTC/HCC)

Follow-up includes:

- Clinical exam.
- Neck ultrasound.
- Thyroglobulin (Tg) for total thyroidectomy patients.
- Anti-Tg antibodies.
- RAI scans for high-risk patients.

Dynamic Risk Stratification

Assessed at 12 months:

- **Excellent response**: <5% recurrence.
- **Indeterminate response**: ~20% recurrence.
- **Biochemical incomplete**: detectable Tg.

Sam Mosleh, MD.

- **Structural incomplete**: persistent disease.

Guides intensity of follow-up.

Medullary Thyroid Carcinoma

Follow-up markers:

- Calcitonin.
- CEA.
- Doubling times (major prognostic indicator).

Imaging:

- Ultrasound.
- CT/MRI.
- PET for metastatic disease.

Patterns of Recurrence

- **PTC**: cervical lymph nodes.
- **FTC**: distant metastases (lung, bone).
- **HCC**: distant metastases (lung, bone, liver).
- **MTC**: cervical nodes, mediastinum, liver, lungs.

Board-Favorite Cross-Cutting Pearls

- Ultrasound is the **primary imaging** for thyroid and cervical nodes.
- CT with contrast is safe and essential for staging invasive disease.
- FNA cannot diagnose **FTC or HCC** — requires capsular/vascular invasion.
- RAI is **not** used for MTC or most HCC.
- Total thyroidectomy has **double** the complication rate of lobectomy.
- Central neck dissection is **therapeutic**, not prophylactic (except MTC).
- Calcitonin doubling time is the **strongest prognostic factor** in MTC.
- Tg is **not reliable** after lobectomy.
- Dynamic risk stratification guides long-term follow-up intensity.

Anaplastic Thyroid Carcinoma (ATC)

Overview

Anaplastic thyroid carcinoma is one of the most aggressive solid tumors in humans. It arises from **follicular epithelium**, often through **dedifferentiation** of pre-existing PTC/FTC, though it can also occur **de novo**.

Key characteristics from the document:

- **Extremely rare**: ~1–2 cases per million annually.
- **Highly lethal**: despite being only 1% of thyroid cancers, it accounts for **up to 35% of thyroid cancer deaths**.

Sam Moslemi, M.D.

- **Typical age**: mean ~65 years.
- **Female predominance**.
- **Rapid progression**, large tumor size at presentation, and early local invasion.
- **Stage IV at diagnosis** by definition (AJCC 8th edition).

"Although it comprises only 1% of all thyroid cancers, ATC has significant mortality and accounts for up to 35% of all deaths from thyroid cancer."

Epidemiology & Risk Factors

- Elderly patients (peak in 60s–70s).
- More common in women.
- May arise from pre-existing differentiated thyroid cancer (especially tall-cell PTC).
- Risk factors include:
  - Prior radiation exposure
  - Long-standing goiter
  - Chronic thyroid disease
  - Family history of thyroid disease

Clinical Presentation

ATC classically presents with **rapidly enlarging neck mass**.

Findings from the document:

- Large, firm, immobile thyroid mass.
- Often >5 cm at presentation.
- Pain or tenderness possible.
- Local invasion common: muscles, trachea, esophagus, larynx.
- Symptoms:
  - Hoarseness
  - Dysphagia
  - Dyspnea
  - Stridor
  - Cough
  - Hemoptysis
- Vocal cord paralysis on laryngoscopy is common.
- Substernal extension may occur.

"The most frequent symptoms are hoarseness, dysphagia, dyspnea, and stridor."

Airway Evaluation

Because airway compromise is a major cause of mortality, airway assessment is essential.

Recommended evaluations:

- Physical exam
- **Fiber-optic laryngoscopy** (vocal cord mobility)
- **Bronchoscopy** (if airway invasion suspected)
- **CT neck with contrast** (critical for mapping invasion)

Laboratory Findings

- Thyroid function usually normal.

Sam Mosleh, MD

- Some cases show thyrotoxicosis due to tumor-induced inflammation.
- Labs may show elevated inflammatory markers.

Imaging

Ultrasound

- Initial evaluation of thyroid and cervical nodes.
- ATC appears heterogeneous, ill-defined, often with necrosis.

CT Neck/Chest with Contrast

Most important imaging modality for ATC.

- Defines invasion of:
  - Trachea
  - Esophagus
  - Larynx
  - Carotid sheath
  - Mediastinum
- Evaluates nodal disease and lung metastases.

"High-resolution cross-sectional imaging is critical for surgical planning."

PET/CT

Useful for staging and detecting distant metastases.

Pathology

ATC shows:

- High mitotic activity
- Bizarre multinucleated giant cells
- Spindle cells
- Extensive necrosis
- Loss of thyroid differentiation markers

"There is usually extensive necrosis, often so diffuse that the only viable tumor is preserved around blood vessels."

Coexistent differentiated thyroid carcinoma (often tall-cell PTC) is common.

Molecular Profile

ATC has a **high mutational burden**.

Common mutations:

- **TP53** (most frequent)
- **BRAF V600E** (~50% of cases)
- **RAS**
- **PIK3CA**
- **PTEN**
- **RET fusions** (rare but actionable)
- **NTRK fusions** (rare but actionable)

"Genomic testing and mutational tumor burden are now imperative recommended initial diagnostic studies."

Staging (AJCC 8th Edition)

All ATC is **Stage IV**, subdivided:

- **IVA**: Intrathyroidal disease
- **IVB**: Gross extrathyroidal extension or nodal metastases

Sam Moslemi, MD.

- **IVC**: Distant metastases

T-stage:

- T1 ≤2 cm
- T2 2–4 cm
- T3 >4 cm or minimal ETE
- T4a invasion into strap muscles, larynx, trachea, esophagus
- T4b invasion into prevertebral fascia or encasing carotid artery

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Treatment Overview

ATC treatment is **multimodal**, combining:

- Surgery (when feasible)
- External beam radiation
- Systemic therapy (chemotherapy, targeted therapy, immunotherapy)

RAI is **not effective**.

"Poorly differentiated or undifferentiated tumors cannot concentrate iodine… radioactive iodine treatment is not effective."

Surgery

Surgery is considered **only when complete or near-complete resection is feasible**.

Indications

- Stage IVA (intrathyroidal)
- Selected Stage IVB (resectable extrathyroidal extension)

Goals

- R0 or R1 resection
- En-bloc resection when possible
- Avoid incomplete (R2) resection unless for palliation

"Primary surgical resection can be considered for patients with stage IVA or IVB disease… when gross resection (R1) is anticipated."

Contraindications

- Unresectable invasion of:
  - Carotid artery
  - Prevertebral fascia
  - Mediastinal structures
- Distant metastases with poor performance status

Radiation Therapy

External beam radiation is a core component of treatment.

Used:

- Postoperatively
- Definitively when surgery is not possible
- With radiosensitizing chemotherapy

Systemic Therapy

Targeted Therapy (Revolutionized ATC Management)

BRAF V600E–Mutated ATC

- **Dabrafenib + Trametinib**
  - Response rate: **69%**
  - 12-month OS: **80%**
  - FDA-approved for BRAF-mutant ATC

Sam Moslemi, MD

"This data led to the FDA approval… the first newly approved therapy for ATC in ~50 years."

NTRK Fusion–Positive ATC

- **Larotrectinib**
- **Entrectinib**

RET Fusion–Positive ATC

- **Selpercatinib**
- **Lenvatinib** (less specific)

High Tumor Mutational Burden

- **Pembrolizumab** may be effective.

Chemotherapy

Traditional regimens have limited benefit but may be used with radiation.

Neoadjuvant Therapy

A major paradigm shift:

- BRAF/MEK inhibitors can **convert unresectable tumors to resectable**.
- Dramatic responses allow:
  - Avoidance of tracheostomy
  - Improved quality of life
  - Complete surgical resection

"Complete surgical resection was only possible after meaningful clinical response… changing the paradigm for treating ATC."

Thyroid Lymphoma & Metastases (Brief Integration)

Thyroid Lymphoma

- Usually, DLBCL or MALT.
- Strong association with Hashimoto's.
- Treated primarily with **R-CHOP** ± radiation.
- Surgery rarely indicated.

Metastases to Thyroid

Common primaries:

- Renal cell carcinoma
- Lung
- Colorectal
- Breast
- Melanoma

Surgery considered for:

- Isolated metastasis
- Airway compromise
- Local control

Prognosis

ATC has extremely poor prognosis without targeted therapy.

- Median survival historically: **3–6 months**
- With modern targeted therapy: significantly improved in selected patients

Major causes of death:

- Airway obstruction
- Catastrophic hemorrhage
- Local invasion
- Distant metastases

Board-Favorite ATC Pearls

- Rapidly enlarging neck mass in elderly → ATC until proven otherwise.

Sam Moslemi, M.D.

- Always evaluate airway early (laryngoscopy, CT).
- FNA may be nondiagnostic → core biopsy or open biopsy.
- ATC does **not** take up RAI.
- All ATC is **Stage IV**.
- BRAF V600E mutation → dabrafenib + trametinib (dramatic responses).
- NTRK/RET fusions → targeted therapy.
- Surgery only if R0/R1 resection feasible.
- Multimodal therapy improves survival.
- Thyroid lymphoma can mimic ATC but responds rapidly to steroids/chemotherapy.

Primary Thyroid Lymphoma (PTL)

Overview

Primary thyroid lymphoma (PTL) is a **rare extranodal non-Hodgkin lymphoma** arising in the thyroid gland. It represents:

- ~2% of all extranodal lymphomas
- ~1–5% of all thyroid malignancies

Two major subtypes dominate:

- **Diffuse large B-cell lymphoma (DLBCL)** — ~70%, aggressive
- **MALT lymphoma** — ~25%, indolent

"When considering all extranodal lymphomas, only about 2% occur in the thyroid gland… DLBCL comprises approximately 70% of cases… MALT up to 25%."

Strong association with **Hashimoto's thyroiditis**:

- ~50% of PTL patients have a history of Hashimoto's
- ~⅔ show histologic evidence of chronic lymphocytic thyroiditis

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Epidemiology & Risk Factors

- Mean age at diagnosis: **~65 years**
- Female predominance
- Strong link to **chronic autoimmune thyroiditis**
- Rarely associated with Graves' disease or other autoimmune conditions

Mechanism: chronic antigenic stimulation → lymphoid proliferation → malignant transformation.

Clinical Presentation

PTL often mimics anaplastic thyroid carcinoma (ATC) because both present with **rapidly enlarging neck masses**.

Common features:

- Rapid neck swelling

Sam Moslemi, MD

- Firm, sometimes tender thyroid mass
- Often fixed to adjacent structures
- Substernal extension common
- Compressive symptoms:
  - Hoarseness
  - Dysphagia
  - Dyspnea
  - Stridor

"Because of the rapid progression and large size, local invasion is frequently seen… hoarseness, dysphagia, dyspnea, and stridor."

Differentiating Features from ATC

- **B symptoms** (fever, night sweats, weight loss) in ~10%
- History of Hashimoto's
- Thyroid function abnormalities more common (10%)
- Less necrosis and less cytologic pleomorphism than ATC

Diagnostic Workup

History

- Rapidly enlarging mass
- B symptoms
- Hashimoto's thyroiditis history
- Prior autoimmune disease
- Prior malignancy (to rule out metastasis)

Physical Exam

- Large, firm, often fixed mass
- Cervical lymphadenopathy
- Airway symptoms → urgent evaluation

Airway Evaluation

- **Fiber-optic laryngoscopy** for vocal cord mobility
- **Bronchoscopy** if airway invasion suspected
- **Esophagoscopy** if dysphagia/odynophagia

"Bronchoscopy is useful for determining extent of disease… evaluation of the tracheal lumen."

Imaging

Ultrasound

- Hypoechoic, pseudocystic pattern
- Often asymmetric
- Useful for guiding biopsy

CT Neck/Chest with Contrast

- Defines extent of invasion
- Evaluates mediastinal nodes
- Helps differentiate from ATC

PET/CT

- Used for staging DLBCL
- MALT may be less FDG-avid

Biopsy & Pathology

FNA

- Often **suggestive** but **not diagnostic**
- Shows monomorphic lymphoid population
- High N:C ratio
- Requires immunophenotyping

Sara Moslemi, MD

"FNA can suggest lymphoma, but typically is nondiagnostic."

Core Needle Biopsy

- Preferred initial diagnostic test
- Allows immunohistochemistry and flow cytometry
- Sensitivity ~97%, specificity ~87% for B-cell lymphoma

Open Surgical Biopsy

- Reserved for:
  - Nondiagnostic FNA/core
  - Need for full architectural assessment
  - Subtype determination when treatment depends on it

Staging

Lugano Staging System

Used for all extranodal lymphomas.

Distribution in PTL:

- **Stage IE** (thyroid only): ~50%
- **Stage IIE** (thyroid + regional nodes): ~45%
- **Stage IIIE/IV** (distant disease): ~5%

"Almost 80% of patients have limited disease on presentation."

Treatment

General Principles

- **Surgery is NOT primary treatment**
- PTL is highly **chemosensitive** and **radiosensitive**
- Rapid response to therapy often avoids tracheostomy

DLBCL (Aggressive)

Preferred regimen: R-CHOP

- Rituximab
- Cyclophosphamide
- Doxorubicin
- Vincristine
- Prednisolone

Radiation added for limited disease (Stage IE/IIE).

"Combined chemotherapy and radiation therapy for limited lymphoma is associated with higher survival."

MALT Lymphoma (Indolent)

- Radiation alone may be curative for localized disease
- R-CHOP for disseminated or transformed disease

Airway Compromise

- Symptoms often improve **within hours** of starting steroids in R-CHOP
- Tracheostomy usually avoided

"Obstructive symptoms… improve within hours of initiating R-CHOP because of steroid action."

Surgery

Not recommended except for:

- Diagnostic biopsy when less invasive methods fail

Sam Mosleh, MD.

- Rare cases of isolated mass causing airway obstruction not responsive to medical therapy

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Prognosis

- Generally favorable, especially for MALT
- DLBCL prognosis depends on stage and response to therapy
- Early diagnosis and rapid initiation of therapy are critical

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Board-Favorite PTL Pearls

- Rapidly enlarging thyroid mass → think **ATC vs lymphoma**.
- Hashimoto's is a major risk factor for PTL.
- B symptoms suggest lymphoma, not ATC.
- FNA often nondiagnostic → core biopsy preferred.
- R-CHOP is the mainstay for DLBCL.
- Radiation alone may cure localized MALT.
- Surgery is rarely indicated.
- Steroids rapidly improve airway symptoms.
- PET/CT used for staging DLBCL.
- Most PTL presents as Stage IE or IIE.

Metastases to the Thyroid Gland

Overview

Metastatic disease to the thyroid gland is **uncommon**, but clinically important. It must always be considered when a patient with a thyroid mass has a **history of malignancy**, even if remote.

Key points from the document:

- Found in **1–3%** of patients undergoing thyroid surgery for suspected cancer.
- Can be **synchronous** or **metachronous**.
- Mean interval for metachronous metastasis is **~6 years**.
- Most common primaries:
  - **Renal cell carcinoma (RCC)** — most common
  - Lung carcinoma
  - Colorectal carcinoma
  - Breast carcinoma
  - Melanoma

"The most commonly reported malignancies with metastases to the thyroid are renal cell carcinoma (RCC) and lung, colorectal, and breast carcinoma."

Rare primaries reported include:

- Urothelial carcinoma
- Endometrial carcinoma
- GIST

Sam Moslemi, MD

- Pancreatic intraductal papillary mucinous carcinoma
- Ovarian carcinoma
- Testicular seminoma
- Uterine carcinoma

Epidemiology & Pathophysiology

The thyroid is highly vascular, yet metastases are rare. Proposed reasons:

- High oxygen and iodine content may inhibit tumor implantation.
- Rapid blood flow may prevent metastatic seeding.

However, abnormal thyroid tissue (goiter, thyroiditis) may increase susceptibility.

"An abnormal thyroid gland may increase the likelihood of metastatic deposits."

Clinical Presentation

Metastases can mimic primary thyroid malignancy.

Common presentations:

- New or enlarging thyroid nodule
- Neck swelling
- Dysphagia
- Dysphonia
- Cough

Less common:

- Rapid enlargement (can mimic ATC or lymphoma)
- Incidental discovery on imaging or postoperative pathology (~25%)

"Up to 25% of cases… are incidentally found."

Symptoms depend on:

- Tumor size
- Local invasion
- Primary tumor biology

Diagnostic Workup

History

Critical to ask about:

- Prior malignancy (even >10 years ago)
- RCC history (most common source)
- Lung, colorectal, breast, melanoma history

"Thyroid metastases can present many years after initial diagnosis… mean interval ~6 years."

Physical Exam

- Thyroid nodule or mass
- Possible cervical lymphadenopathy
- Signs of invasion (rare compared to ATC)

Ultrasound

Findings are variable:

- Solid, hypoechoic nodules
- Irregular margins
- Hypervascularity
- May resemble primary thyroid cancer

FNA Cytology

Sam Moslemi, MD

Accuracy is limited:

- Correct in ~75% of cases
- Misdiagnosis as primary thyroid cancer in ~25%

"In 25%, the FNA diagnosed primary thyroid malignancy instead of metastatic disease."

When prior cancer history exists, cytology must be interpreted with caution.

Core Needle Biopsy

Improves diagnostic accuracy.

Pathology Review

Comparison with prior tumor pathology is essential.

Imaging

CT Neck/Chest with Contrast

Indications:

- Large or rapidly enlarging mass
- Suspected invasion
- Preoperative planning

PET/CT

Useful for:

- Identifying other metastatic sites
- Staging systemic disease

Treatment Principles

Management depends on:

- Extent of systemic disease
- Symptoms
- Local invasion
- Patient performance status
- Primary tumor biology

Surgery

Surgery is considered in selected cases:

Indications:

- Isolated metastasis to thyroid
- Symptomatic local disease (airway compromise, dysphagia)
- Need for local control
- Diagnostic uncertainty

Procedures:

- Thyroid lobectomy
- Total thyroidectomy
- Metastectomy (for isolated lesions)

"Thyroid lobectomy or total thyroidectomy is usually considered… with the aim of long-term cure or achieving local control."

Not indicated when:

- Widespread metastatic disease with poor prognosis
- Surgery will not improve symptoms or quality of life

Non-Surgical Management

- Systemic therapy based on primary tumor
- Radiation for palliation
- Close surveillance for asymptomatic patients

Special Considerations by Primary Tumor

Renal Cell Carcinoma (RCC)

Sam Mosleh, MD

- Most common source of thyroid metastasis
- Often hypervascular
- May present many years after nephrectomy
- Surgery often considered for isolated metastasis

Lung Cancer

- Often part of widespread disease
- Surgery rarely indicated

Colorectal Cancer

- Less common but documented
- Surgery considered for isolated metastasis

Breast Cancer

- Usually part of systemic spread
- Managed with systemic therapy

Melanoma

- Aggressive biology
- Surgery only for isolated lesions

Prognosis

Prognosis depends entirely on the **primary tumor** and **extent of systemic disease**, not the thyroid metastasis itself.

Better prognosis:

- Isolated RCC metastasis
- Long disease-free interval
- Good performance status

Poor prognosis:

- Widespread metastases
- Aggressive primaries (melanoma, lung)

Board-Favorite Pearls

- RCC is the **most common** tumor to metastasize to the thyroid.
- Metastases may appear **years after** primary cancer treatment.
- FNA may misdiagnose metastasis as primary thyroid cancer.
- Always compare cytology with prior tumor pathology.
- Surgery is considered for **isolated metastasis** or **airway compromise**.
- Up to **25%** of metastases are found **incidentally** after thyroidectomy.
- Abnormal thyroid tissue (goiter, thyroiditis) may increase metastatic seeding.

Integrated Surgical & Oncologic Management Algorithms

Algorithm 1 — Initial Evaluation of a Thyroid Mass

Step 1: Clinical Assessment

- History: growth rate, radiation exposure, family history,

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autoimmune disease, prior malignancy.
- Symptoms:
  - Hoarseness → RLN involvement (PTC, ATC, lymphoma).
  - Rapid growth → ATC or lymphoma.
  - B symptoms → lymphoma.
  - Hemoptysis → ATC or invasive disease.
- Physical exam:
  - Fixed mass → ATC, lymphoma, invasive PTC.
  - Cervical nodes → PTC, ATC, MTC.

Step 2: Airway Evaluation
- Fiber-optic laryngoscopy for vocal cord mobility.
- Bronchoscopy if airway invasion suspected.
- CT neck with contrast for mapping invasion.
  - Document notes: "High-resolution cross-sectional imaging is critical for surgical planning."

Step 3: Ultrasound
- Evaluate thyroid and central/lateral nodes.
- Hypoechoic pseudocystic pattern → lymphoma.
- Heterogeneous necrotic mass → ATC.

Step 4: Biopsy Strategy
- FNA for most nodules.
- If rapidly growing mass → **core biopsy** preferred.
- If FNA nondiagnostic → **open biopsy** (ATC, lymphoma).
  - Document: "If FNA results are limited or nondiagnostic, open biopsy should be performed."

Step 5: Molecular Testing
- PTC/FTC/HCC: BRAF, RAS, RET/PTC, PAX8-PPARγ.
- MTC: **RET germline testing mandatory**.
- ATC: **BRAF V600E, NTRK, RET fusion, RAS, high mutational load**.
  - Document: "Genomic testing and mutational tumor burden are now imperative."

Algorithm 2 — Differentiated Thyroid Cancer (PTC/FTC/HCC)

Step 1: Determine Risk Category
- Low-risk: tumor <4 cm, no gross ETE, no nodal disease.

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- High-risk: >4 cm, gross ETE, clinically positive nodes, distant mets.

Step 2: Choose Extent of Surgery

- **Lobectomy** for low-risk PTC and minimally invasive FTC.
- **Total thyroidectomy** for:
  - Tumor >4 cm
  - Gross ETE
  - Nodal disease
  - Vascular invasion (FTC/HCC)
  - Hürthle cell carcinoma >4 cm or invasive

Step 3: Nodal Management

- Central neck dissection:
  - **Therapeutic only** for PTC/FTC/HCC.
  - **Not prophylactic** except in invasive PTC.
- Lateral neck dissection:
  - Only for clinically/radiologically involved nodes.

Step 4: RAI Decision

- Indicated for:
  - High-risk PTC
  - Widely invasive FTC
  - Vascular invasion
  - Distant metastases
- Not effective in:
  - Hürthle cell carcinoma (often RAI-resistant)
  - ATC
  - MTC

Step 5: Follow-Up

- Tg and anti-Tg (after total thyroidectomy).
- Ultrasound at 6–12 months.
- Dynamic risk stratification at 12 months.

Algorithm 3 — Medullary Thyroid Carcinoma (MTC)

Step 1: Mandatory Pre-Op Testing

- **RET germline testing**.
- **Rule out pheochromocytoma** (plasma metanephrines).
  - Must treat pheo **before** thyroid surgery.

Step 2: Imaging

- Ultrasound for thyroid and nodes.
- CT/MRI for advanced disease.
- PET for metastases.

Step 3: Surgery

- **Total thyroidectomy + central neck dissection** for all MTC.
- Lateral neck dissection if:
  - Calcitonin >200 pg/mL
  - Imaging shows nodal disease

Step 4: No RAI

- MTC does not take up iodine.

Step 5: Follow-Up

- Calcitonin and CEA doubling times (major prognostic factor).
- Imaging for recurrence.

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Algorithm 4 — Anaplastic Thyroid Carcinoma (ATC)

Step 1: Immediate Priorities

- Airway evaluation (laryngoscopy, CT).
- Core biopsy for diagnosis.
- Molecular testing: BRAF, NTRK, RET fusion, RAS, TP53, tumor mutational burden.

Step 2: Determine Resectability

- **Resectable (Stage IVA/IVB)**:
  - Surgery if R0/R1 achievable.
  - En-bloc resection for extrathyroidal invasion.
- **Unresectable**:
  - Neoadjuvant targeted therapy (BRAF/MEK if V600E).
  - Radiation ± chemotherapy.

Document:
"Primary surgical resection can be considered for stage IVA or IVB… when gross resection (R1) is anticipated."

Step 3: Systemic Therapy

- **BRAF V600E** → dabrafenib + trametinib (69% response).
- **NTRK fusion** → larotrectinib or entrectinib.
- **RET fusion** → selpercatinib.
- **High TMB** → pembrolizumab.

Step 4: Radiation

- Often combined with systemic therapy.

Step 5: Palliative Care

- Tracheostomy if airway compromise not responsive to therapy.
- Symptom control for pain, bleeding, obstruction.

Algorithm 5 — Primary Thyroid Lymphoma

Step 1: Diagnosis

- Core biopsy with flow cytometry.
- FNA often nondiagnostic.
- PET/CT for staging (DLBCL).

Step 2: Determine Subtype

- DLBCL (aggressive).
- MALT (indolent).

Step 3: Treatment

- **DLBCL** → R-CHOP ± radiation.
- **MALT** → radiation alone for localized disease.

Document:
"Obstructive symptoms improve within hours of initiating R-CHOP because of steroid action."

Step 4: Surgery

- Rarely indicated except for diagnosis or airway compromise.

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Algorithm 6 — Metastases to the Thyroid

Step 1: Identify Primary

Most common:

- RCC
- Lung
- Colorectal
- Breast
- Melanoma

Step 2: Diagnostic Workup

- FNA (75% accurate).
- Core biopsy if needed.
- Compare with prior tumor pathology.

Step 3: Determine Extent of Disease

- PET/CT for systemic staging.
- CT neck for local invasion.

Step 4: Treatment

- **Isolated metastasis →** thyroid lobectomy or total thyroidectomy.
- **Symptomatic local disease →** surgery for airway/dysphagia relief.
- **Widespread disease →** systemic therapy based on primary tumor.

Document:

"Thyroid lobectomy or total thyroidectomy is usually considered… with the aim of long-term cure or achieving local control."

Algorithm 7 — Rapidly Enlarging Thyroid Mass (Critical Board Topic)

Differential

- ATC
- Thyroid lymphoma
- Metastasis (RCC)
- Hemorrhage into a nodule
- Rarely: aggressive PTC variants

Workup

- Immediate airway evaluation
- CT neck with contrast
- Core biopsy
- Labs: TSH, CBC, LDH (lymphoma), calcium
- Consider B symptoms

Key Distinguishers

- **ATC**: necrosis, bizarre cells, rapid invasion
- **Lymphoma**: Hashimoto's history, B symptoms, pseudocystic US
- **Metastasis**: prior cancer history

Algorithm 8 — Airway Threat in Thyroid Malignancy

Signs

- Stridor
- Dyspnea
- Hemoptysis
- Vocal cord paralysis
- Tracheal deviation or compression

Sam Moslemi, MD

Immediate Steps

- Laryngoscopy
- CT neck
- Bronchoscopy if needed

Condition-Specific Management

- **ATC**: targeted therapy → rapid shrinkage; tracheostomy if needed.
- **Lymphoma**: steroids + R-CHOP → rapid improvement.
- **PTC/FTC**: surgery if compressive.
- **Metastasis**: surgery for palliation.

Board-Favorite Integrated Pearls

- Rapid enlargement → ATC or lymphoma until proven otherwise.
- Hashimoto's + rapid mass → lymphoma.
- Prior RCC + thyroid mass → metastasis.
- MTC → always rule out pheochromocytoma first.
- ATC → all Stage IV; molecular testing mandatory.
- Hürthle cell carcinoma → RAI-resistant.
- FTC → hematogenous spread; vascular invasion predicts prognosis.
- PTC → lymphatic spread; excellent prognosis.
- Lymphoma → treat with R-CHOP, not surgery.

Ultra-High-Yield Board Pearls & Rapid Review

Papillary Thyroid Carcinoma (PTC) — High-Yield Pearls

- Most common thyroid cancer; excellent prognosis (10-yr survival ~99%).
- Lymphatic spread common; distant mets rare (lungs > bone).
- BRAF V600E associated with aggressive variants (tall cell).
- Lobectomy adequate for low-risk tumors <4 cm without ETE or nodal disease.
- Total thyroidectomy for >4 cm, gross ETE, nodal disease, or high-risk features.
- Central neck dissection **therapeutic only**, except in invasive disease.
- RAI not routinely indicated for low-risk PTC.
- Dynamic risk stratification at 12 months predicts recurrence (<5% if excellent response).

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- Active surveillance acceptable for microPTC (<1 cm) in selected patients.

Follicular Thyroid Carcinoma (FTC) — High-Yield Pearls

- Hematogenous spread (lungs, bone) — **key differentiator** from PTC.
- Diagnosis requires **capsular and/or vascular invasion** (cannot diagnose on FNA).
- Minimally invasive FTC → lobectomy adequate.
- Widely invasive FTC → total thyroidectomy + RAI.
- Vascular invasion is the strongest predictor of recurrence and mortality.
- More common in iodine-deficient regions.

Hürthle Cell Carcinoma (HCC) — High-Yield Pearls

- Oncocytic variant; now considered a distinct entity.
- More aggressive than FTC; higher recurrence and metastasis rates.
- Less RAI-avid → RAI often ineffective.
- Minimally invasive HCC → lobectomy acceptable.
- Widely invasive or >4 cm → total thyroidectomy.
- Distant metastases more common (lung, bone, liver).

Medullary Thyroid Carcinoma (MTC) — High-Yield Pearls

- Neuroendocrine tumor from **C-cells**; secretes **calcitonin**.
- 20–25% hereditary (MEN2A, MEN2B, FMTC).
- **RET germline testing mandatory** for all patients.
- Must **rule out pheochromocytoma before thyroid surgery**.
- Treatment: **total thyroidectomy + central neck dissection**.
- Lateral neck dissection if calcitonin >200 pg/mL or imaging positive.
- RAI ineffective.
- Calcitonin and CEA **doubling times** are major prognostic markers.
- MEN2B (RET M918T) is the most aggressive form.

Anaplastic Thyroid Carcinoma (ATC) — High-Yield Pearls

- One of the most aggressive human cancers; all cases are **Stage IV**.

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- Presents with rapidly enlarging neck mass, hoarseness, dyspnea, stridor.
- Airway evaluation is urgent (laryngoscopy, CT).
- FNA often nondiagnostic → core biopsy or open biopsy.
- Molecular testing essential: **BRAF V600E, NTRK, RET fusion, RAS, TP53, TMB**.
- **BRAF V600E** → dabrafenib + trametinib (dramatic responses).
- NTRK fusion → larotrectinib/entrectinib.
- RET fusion → selpercatinib.
- High TMB → pembrolizumab.
- Surgery only if R0/R1 resection feasible (Stage IVA/IVB).
- RAI ineffective.
- Mortality from airway obstruction, hemorrhage, local invasion.

Primary Thyroid Lymphoma — High-Yield Pearls

- Strong association with **Hashimoto's thyroiditis** (~50%).
- Two major types: DLBCL (aggressive), MALT (indolent).
- Rapidly enlarging mass → mimics ATC.
- B symptoms in ~10%.
- FNA often nondiagnostic → **core biopsy with flow cytometry** preferred.
- Treatment:
  - DLBCL → **R-CHOP ± radiation**.
  - MALT → radiation alone for localized disease.
- Steroids rapidly improve airway symptoms.
- Surgery rarely indicated.

Metastases to the Thyroid — High-Yield Pearls

- Occur in 1–3% of thyroid surgeries for suspected cancer.
- Most common primary: **renal cell carcinoma (RCC)**.
- Others: lung, colorectal, breast, melanoma.
- Can appear many years after primary tumor (mean ~6 years).
- FNA correct in ~75%; misdiagnosis as primary thyroid cancer in ~25%.
- Surgery considered for isolated metastasis or airway compromise.
- Abnormal thyroid tissue (goiter, thyroiditis) increases metastatic seeding.

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Rapid-Fire Differentials (Boards Love These)

Rapidly Enlarging Thyroid Mass

- ATC
- Thyroid lymphoma
- Metastasis (RCC)
- Hemorrhage into a nodule

Thyroid Mass + B Symptoms

- Thyroid lymphoma

Thyroid Mass + Prior RCC

- Metastasis to thyroid

Thyroid Mass + Diarrhea/Flushing

- MTC

Thyroid Mass + Hypercalcemia

- MTC (rare, from ectopic PTHrP)
- Parathyroid carcinoma (if separate mass)

Thyroid Mass + Vocal Cord Paralysis

- ATC
- Invasive PTC
- Lymphoma

Most Common Lists (High-Yield Memory Anchors)

Most Common Thyroid Cancer

- PTC

Most Common Cause of Thyroid Metastasis

- RCC

Most Common Thyroid Lymphoma

- DLBCL

Most Common Cause of Death in ATC

- Airway obstruction

Most Common Site of Distant Mets

- PTC: lungs
- FTC: bone > lungs
- HCC: lung, bone, liver
- MTC: liver, lungs, bone
- ATC: lungs

Surgical Indications Summary

- **PTC low-risk** → lobectomy
- **PTC high-risk** → total thyroidectomy
- **Minimally invasive FTC/HCC** → lobectomy
- **Widely invasive FTC/HCC** → total thyroidectomy
- **MTC** → total thyroidectomy + central neck dissection
- **ATC** → surgery only if R0/R1 feasible
- **Lymphoma** → no surgery (except biopsy)
- **Metastasis** → surgery for isolated lesion or airway compromise

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Ultra-Condensed "One-Liners" for Boards

- PTC spreads lymphatically; FTC spreads hematogenously.
- Hürthle cell carcinoma is RAI-resistant.

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- MTC requires RET testing and pheo exclusion before surgery.
- ATC is always Stage IV and needs molecular testing immediately.
- Thyroid lymphoma responds rapidly to steroids and R-CHOP.
- RCC is the most common metastasis to the thyroid.
- FNA cannot diagnose FTC or HCC — need capsular/vascular invasion.
- Dynamic risk stratification predicts recurrence better than initial staging.
- BRAF V600E mutation dramatically changes ATC management.

Thyroidectomy & Neck Dissection

Overview

Thyroid surgery requires mastery of anatomy, nerve preservation, parathyroid protection, and oncologic compartment-based lymphadenectomy. This section covers operative indications, techniques, and complications in the same high-yield format as the cancer sections.

Epidemiology / Indications

Indications for Thyroidectomy

- **Differentiated thyroid cancer (per risk stratification).**
- **Medullary thyroid carcinoma (total thyroidectomy + central neck).**
- **Anaplastic thyroid carcinoma (only if R0/R1 feasible).**
- **Symptomatic benign disease (compressive goiter, substernal extension).**
- **Toxic nodular goiter or Graves' (selected cases).**
- **Indeterminate nodules (diagnostic lobectomy).**

Indications for Neck Dissection

- **Therapeutic only for PTC/FTC/HCC (clinically/radiologically positive nodes).**
- **Mandatory central neck dissection for MTC.**
- **Not indicated for benign disease.**
- **Not prophylactic in PTC except select high-risk invasive tumors.**

Surgical Anatomy (High-Yield)

Recurrent Laryngeal Nerve (RLN)

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- **Runs in tracheoesophageal groove.**
- **Enters larynx at cricothyroid joint.**
- **Most vulnerable at Berry's ligament.**

External Branch of Superior Laryngeal Nerve (EBSLN)

- **Runs with superior thyroid vessels.**
- **Controls cricothyroid muscle → pitch elevation.**
- **At risk during superior pole ligation.**

Parathyroid Glands

- **Usually 4; posterior surface.**
- **Inferior glands variable.**
- **Blood supply from inferior thyroid artery branches.**

Key Vascular Structures

- **Superior thyroid artery (ECA).**
- **Inferior thyroid artery (thyrocervical trunk).**
- **Middle thyroid vein (IJV).**

Preoperative Evaluation

Laryngoscopy

- **Mandatory to document vocal cord mobility.**
- **Identifies pre-existing RLN palsy.**

Imaging

- **Ultrasound for thyroid + nodes.**
- **CT neck/chest for large goiters, substernal extension, invasive tumors.**
- **MRI if contrast contraindicated.**

Labs

- **TSH, calcium, vitamin D.**
- **Calcitonin/CEA for MTC.**
- **Thyroglobulin for DTC surveillance (not pre-op).**

Operative Techniques

Thyroid Lobectomy

Indications

- **Low-risk PTC (<4 cm, no ETE, no nodes).**
- **Minimally invasive FTC/HCC.**
- **Indeterminate nodules (diagnostic).**
- **Selected benign disease.**

Advantages

- **Lower RLN injury risk.**
- **Lower hypocalcemia risk.**
- **Less lifelong hormone dependence.**

Total Thyroidectomy

Indications

- **High-risk PTC (>4 cm, ETE, nodes).**
- **Widely invasive FTC/HCC.**
- **All MTC.**
- **Bilateral disease.**

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- **Graves' with large goiter or ophthalmopathy.**
- **Need for RAI therapy.**

Risks

- **Higher RLN injury.**
- **Higher hypocalcemia.**
- **Higher bleeding risk.**

Central Neck Dissection (Level VI)

Boundaries

- **Hyoid → innominate artery.**
- **Carotid sheaths laterally.**
- **Prevertebral fascia posteriorly.**

Indications

- **Therapeutic for PTC/FTC/HCC with positive nodes.**
- **Routine for all MTC.**
- **Not prophylactic for PTC except invasive tumors.**

Lateral Neck Dissection (Levels II–V)

Indications

- **Radiologic or biopsy-proven nodal metastases.**
- **MTC with calcitonin >200 pg/mL or imaging-positive nodes.**

Principles

- **Compartment-oriented removal.**
- **No "berry picking."**
- **Preserve SAN, IJV, SCM.**

Intraoperative Nerve Monitoring (IONM)

Uses

- **Identifies RLN.**
- **Confirms functional integrity.**
- **Helpful in:**
  - **Reoperations**
  - **Large goiters**
  - **Invasive cancers**
  - **Anatomic distortion**

Limitations

- **Does not replace meticulous dissection.**
- **Loss of signal requires evaluation for traction/thermal injury.**

Parathyroid Preservation

Strategies

- **Identify visually.**
- **Preserve vascular pedicle.**
- **Avoid cautery near glands.**
- **Autotransplant devascularized glands into SCM.**

Post-op Monitoring

- **Calcium and PTH levels.**
- **Symptoms: perioral numbness, tetany, cramps.**

Complications (High-Yield)

Recurrent Laryngeal Nerve Injury

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Temporary

- **Hoarseness, weak voice.**
- **Usually resolves in weeks–months.**

Permanent

- **Breathiness, aspiration risk.**
- **Bilateral injury → airway compromise → tracheostomy.**

Superior Laryngeal Nerve Injury

- **Loss of high-pitch voice.**
- **Reduced vocal stamina.**
- **Important for singers/teachers.**

Hypocalcemia / Hypoparathyroidism

Temporary

- **~20% after total thyroidectomy.**

Permanent

- **1.8–5%.**

Symptoms

- **Perioral numbness.**
- **Carpopedal spasm.**
- **Chvostek/Trousseau signs.**

Hematoma

- **Life-threatening airway compromise.**
- **Requires immediate bedside decompression.**

Infection

- **Rare due to high vascularity.**

Postoperative Management

Hormone Replacement

- **Levothyroxine after total thyroidectomy.**
- **TSH suppression for high-risk DTC.**

Surveillance

- **Ultrasound at 6–12 months.**
- **Tg/anti-Tg for DTC.**
- **Calcitonin/CEA for MTC.**
- **Imaging for recurrence based on risk.**

Board-Favorite Surgical Pearls

- **RLN most vulnerable at Berry's ligament.**
- **EBSLN at risk during superior pole ligation.**
- **Central neck dissection is therapeutic, not prophylactic (except MTC).**
- **Hematoma → open wound immediately.**
- **Pre-op laryngoscopy is mandatory.**
- **Parathyroid autotransplant if devascularized.**
- **Lateral neck dissection = compartment-oriented, no node picking.**
- **Total thyroidectomy has double the complication rate of lobectomy.**

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- **MTC always requires central neck dissection.**
- **ATC surgery only if R0/R1 feasible.**

Comprehensive Thyroid Disease Algorithms

A — Algorithm: Initial Evaluation of a Thyroid Mass

Step 1 — History

- **Growth rate (rapid → ATC/lymphoma).**
- **Pain (subacute thyroiditis).**
- **B symptoms (lymphoma).**
- **Hyperthyroid symptoms (Graves', toxic nodules).**
- **Hypothyroid symptoms (Hashimoto).**
- **Prior malignancy (metastasis).**
- **Radiation exposure.**
- **Family history (MEN2 → MTC).**

Step 2 — Physical Exam

- **Fixed mass → ATC, lymphoma, invasive PTC.**
- **Tender gland → subacute thyroiditis.**
- **Hard "woody" gland → Riedel.**
- **Cervical nodes → PTC, MTC, ATC.**

Step 3 — Labs

- **TSH (first test).**
- **If hyperthyroid: free T4/T3, TRAb.**
- **If hypothyroid: free T4, TPO antibodies.**
- **If suspicious for MTC: calcitonin, CEA.**

Step 4 — Ultrasound

- **Characterize nodule(s).**
- **Evaluate nodes.**
- **Identify malignancy features (hypoechoic, irregular, microcalcifications, taller-than-wide).**

Step 5 — FNA

- **Based on ATA/TI-RADS.**
- **Indeterminate → molecular testing.**

Step 6 — Additional Imaging

- **CT neck/chest for large goiter, invasion, ATC suspicion.**
- **RAI uptake scan if TSH suppressed.**

B — Algorithm: Hyperthyroidism

Step 1 — Confirm Biochemistry

- **Low TSH + high free T4/T3.**

Step 2 — Determine Etiology

RAI Uptake Scan:

- **Diffuse uptake → Graves'.**
- **Patchy uptake → toxic MNG.**
- **Focal uptake → toxic adenoma.**

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- **Low uptake → thyroiditis (subacute, painless), exogenous hormone.**

Antibodies:

- **TRAb positive → Graves'.**
- **TPO positive → Hashimoto (may have transient hyperthyroid phase).**

Step 3 — Management

- **Graves': antithyroid drugs, RAI, or surgery.**
- **Toxic MNG: RAI or surgery.**
- **Toxic adenoma: RAI or surgery.**
- **Thyroiditis: NSAIDs/steroids; no antithyroid drugs.**

C — Algorithm: Hypothyroidism

Step 1 — Confirm Biochemistry

- **High TSH + low free T4 → overt hypothyroidism.**
- **High TSH + normal free T4 → subclinical hypothyroidism.**

Step 2 — Determine Etiology

- **TPO antibodies → Hashimoto.**
- **Post-surgical or post-RAI.**
- **Medications (amiodarone, lithium).**
- **Central hypothyroidism → low/normal TSH + low free T4.**

Step 3 — Management

- **Treat overt hypothyroidism.**
- **Consider treatment for subclinical depending on symptoms and TSH level.**

D — Algorithm: Thyroiditis

Step 1 — Pain?

- **Painful → subacute (de Quervain).**
- **Painless → Hashimoto, postpartum, silent thyroiditis.**

Step 2 — RAI Uptake

- **Low uptake → thyroiditis.**
- **High uptake → Graves' or toxic nodules.**

Step 3 — ESR/CRP

- **Elevated → subacute thyroiditis.**

Step 4 — Management

- **Subacute: NSAIDs/steroids.**
- **Hashimoto: treat hypothyroidism.**
- **Riedel: biopsy, evaluate for IgG4 disease.**

E — Algorithm: Thyroid Nodule Evaluation

Step 1 — TSH

- **Low → RAI scan.**
- **Normal/high → ultrasound.**

Step 2 — Ultrasound Risk Stratification

- **TI-RADS or ATA.**

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Step 3 — FNA Criteria

- **Based on size + US features.**

Step 4 — FNA Results

- **Benign → surveillance.**
- **Malignant → surgery.**
- **Indeterminate → molecular testing or diagnostic lobectomy.**
- **Non-diagnostic → repeat FNA or core biopsy.**

F — Algorithm: Differentiated Thyroid Cancer (PTC/FTC/HCC)

Step 1 — Confirm Diagnosis

- **FNA cytology.**
- **Molecular testing if indeterminate.**

Step 2 — Staging

- **Ultrasound for nodes.**
- **CT if invasive.**
- **No PET unless aggressive variant.**

Step 3 — Surgical Decision

- **Lobectomy for low-risk PTC (<4 cm, no ETE, no nodes).**
- **Total thyroidectomy for:**
  - **4 cm**
  - **Gross ETE**
  - **Nodal disease**
  - **High-risk histology**
  - **FTC/HCC with vascular invasion**

Step 4 — Nodal Management

- **Central neck dissection therapeutic only.**
- **Lateral neck dissection only if clinically positive.**

Step 5 — RAI Decision

- **High-risk → yes.**
- **Intermediate → selective.**
- **Low-risk → no.**

Step 6 — Follow-Up

- **Tg/anti-Tg.**
- **Ultrasound.**
- **TSH suppression based on risk.**

G — Algorithm: Medullary Thyroid Carcinoma (MTC)

Step 1 — Labs

- **Calcitonin, CEA.**
- **RET germline testing.**

Step 2 — Rule Out Pheochromocytoma

- **Must be addressed before thyroid surgery.**

Step 3 — Imaging

- **Ultrasound for nodes.**
- **CT/MRI for advanced disease.**

Step 4 — Surgery

- **Total thyroidectomy + central neck dissection.**
- **Lateral neck dissection if nodes positive or calcitonin >200 pg/mL.**

Step 5 — Follow-Up

- **Calcitonin/CEA doubling times.**

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H — Algorithm: Anaplastic Thyroid Carcinoma (ATC)

Step 1 — Airway
- **Laryngoscopy.**
- **CT neck.**
- **Bronchoscopy if needed.**

Step 2 — Biopsy
- **Core biopsy or open biopsy.**

Step 3 — Molecular Testing
- **BRAF V600E**
- **NTRK fusion**
- **RET fusion**
- **RAS**
- **TP53**
- **Tumor mutational burden**

Step 4 — Determine Resectability
- **R0/R1 possible → surgery + multimodal therapy.**
- **Unresectable → targeted therapy ± radiation.**

Step 5 — Targeted Therapy
- **BRAF V600E → dabrafenib + trametinib.**
- **NTRK → larotrectinib/entrectinib.**
- **RET → selpercatinib.**
- **High TMB → pembrolizumab.**

I — Algorithm: Thyroid Lymphoma

Step 1 — Presentation
- **Rapid enlargement + Hashimoto history.**

Step 2 — Biopsy
- **Core biopsy with flow cytometry.**

Step 3 — Staging
- **PET/CT.**
- **Lugano staging.**

Step 4 — Treatment
- **DLBCL → R-CHOP ± radiation.**
- **MALT → radiation alone (localized).**

Step 5 — Surgery
- **Only for diagnosis or airway compromise.**

J — Algorithm: Metastases to the Thyroid

Step 1 — History
- **Prior RCC, lung, colorectal, breast, melanoma.**

Step 2 — FNA
- **May misdiagnose → compare with prior pathology.**

Step 3 — Imaging
- **CT neck.**
- **PET/CT for systemic disease.**

Step 4 — Management
- **Isolated metastasis → thyroidectomy/lobectomy.**
- **Widespread disease → systemic therapy based on primary.**

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K — Ultra-High-Yield Algorithm Pearls

- **Rapid enlargement → ATC or lymphoma.**
- **Low TSH → do RAI scan before FNA.**
- **Diffuse uptake → Graves'.**
- **Patchy uptake → toxic MNG.**
- **Focal uptake → toxic adenoma.**
- **Low uptake → thyroiditis.**
- **Hashimoto → lymphoma risk.**
- **MTC → always rule out pheochromocytoma first.**
- **ATC → molecular testing mandatory.**
- **Riedel → mimics ATC.**
- **Central neck dissection is therapeutic, not prophylactic (except MTC).**

Parathyroid

PARATHYROID ANATOMY, PHYSIOLOGY, PATHOPHYSIOLOGY & ULTRASOUND

---

1. Epidemiology & Overview

- Humans typically have **four parathyroid glands**, but number varies (2–6+).
- Primary function: **maintain serum calcium** via PTH.
- Disorders include **primary, secondary, tertiary hyperparathyroidism**, and **hypoparathyroidism**.
- Parathyroid disease is a **top 5 endocrine surgery topic** on ABSITE and boards.
- Surgical success depends on mastery of **embryology, anatomy, ectopic locations, and vascular supply**.

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2. Embryology (Ultra-High Yield)

Branchial Pouch Origins

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- **Superior parathyroids (PIV) → 4th branchial pouch (dorsal wing)**.
- **Inferior parathyroids (PIII) → 3rd branchial pouch (dorsal wing)**.
- **Thymus** → ventral 3rd pouch → descends with PIII as **parathymus complex**.

Migration Path

- **PIII (inferior glands)**: long migration → highly variable final location.
- **PIV (superior glands)**: short migration → consistent location.

Key Embryologic Principles

- Inferior glands descend **with thymus** → ectopic sites along thyrothymic tract.
- Superior glands descend **with ultimobranchial bodies** → paraesophageal/retroesophageal ectopia.
- Timing of separation from thymus determines **inferior gland final position**.
- Crossing of migration paths explains **inferior gland sometimes located above superior gland**.

---

3. Normal Surgical Anatomy

Number, Size, Appearance

- Usually **4 glands**, 30–60 mg each.
- Shape: oval, teardrop, spherical, bilobed.
- Color: **yellow-tan** or **reddish-brown** (lighter than thyroid).
- Texture: soft, pliable.

Superior Parathyroids (PIV)

- **Most constant location** (80%):
  - Posterior thyroid lobe
  - Near cricothyroid junction
  - ~1 cm above RLN–inferior thyroid artery crossing
- Usually in **fatty capsule**, mobile.
- Blood supply: **inferior thyroid artery (80%)**, or posterior branch of superior thyroid artery.

Inferior Parathyroids (PIII)

- **Most variable location** due to long migration.
- Common sites:
  - Lower thyroid pole
  - Thyrothymic ligament
  - Thymic tongue
  - Anterior/posterolateral thyroid
- Blood supply: **inferior thyroid artery**.

Symmetry

- Superior glands symmetric in ~80%.

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- Inferior glands symmetric in ~70%.
- All four symmetric in ~60%.

---

4. Ectopic Parathyroid Anatomy (Critical for Failed Surgery)

Inferior Gland Ectopia (Most Common)

- Along thymic descent path:
  - Carotid sheath
  - Thyrothymic ligament
  - Thymus (most common ectopic site)
  - Mediastinum (anterior > posterior)
- Undescended inferior gland:
  - Above hyoid
  - Beneath mandible
  - Carotid bifurcation

Superior Gland Ectopia

- Retroesophageal
- Paraesophageal
- Retropharyngeal
- High superior pole
- Pyriform sinus (rare)

Intrathyroidal Glands

- 0.5–4% incidence.
- Can be **superior, inferior, or supernumerary**.
- True intrathyroidal gland = fully surrounded by thyroid parenchyma.

Acquired Ectopia

- Enlarged glands migrate downward with gravity and swallowing.
- 40% of superior adenomas found in posterior mediastinal/paraesophageal spaces.

Supernumerary Glands

- Present in 5–13% of individuals.
- Up to 30% in renal hyperplasia cases.
- Common sites: thymus, thyrothymic ligament, carotid sheath, retroesophageal space.
- Rare sites: aortopulmonary window, middle mediastinum, **within vagus nerve**.

---

5. Physiology (Ultra-High Yield)

Cell Types

- **Chief cells** → synthesize & secrete PTH.
- **Oxyphil cells** → mitochondria-rich; increase with age & renal failure; retain sestamibi.

Calcium-Sensing Receptor (CaSR)

- Located on chief cells.
- Low Ca → ↑ PTH secretion.
- High Ca → ↓ PTH secretion + ↑ PTH degradation + ↓ parathyroid proliferation.
- Magnesium also binds CaSR:
  - Mild ↓ Mg → ↑ PTH
  - Severe ↓ Mg → ↓ **PTH** (functional hypoparathyroidism)

PTH Actions

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- **Bone**:
  - Intermittent → anabolic
  - Continuous → catabolic
- **Kidney**:
  - ↑ Ca reabsorption
  - ↓ phosphate reabsorption
  - ↑ 1-α-hydroxylase → ↑ calcitriol
- **GI**:
  - Indirect ↑ Ca absorption via calcitriol

Net Effects

- ↑ Ca
- ↓ Phosphate
- ↑ Calcitriol

---

6. Pathophysiology Overview

Primary Hyperparathyroidism (PHPT)

- Autonomous PTH secretion.
- Causes:
  - Single adenoma (80–85%)
  - Multigland hyperplasia (10–15%)
  - Double adenomas (4%)
  - Parathyroid carcinoma (<1%)
- Variants:
  - Symptomatic
  - Asymptomatic
  - Normocalcemic PHPT
  - Normohormonal PHPT

Secondary Hyperparathyroidism (SHPT)

- Due to chronic hypocalcemia.
- Most common cause: **CKD**.
- Mechanisms:
  - Hyperphosphatemia
  - ↓ 1,25-OH vitamin D
  - ↓ CaSR & VDR expression
  - Skeletal PTH resistance

Tertiary Hyperparathyroidism (THPT)

- Autonomous PTH secretion after long-standing SHPT.
- Seen post-renal transplant.

Hypoparathyroidism

- Most common cause: **post-thyroidectomy** (ischemia or removal).
- Other causes:
  - Autoimmune
  - Riedel's thyroiditis
  - Severe hypomagnesemia
  - Genetic (DiGeorge)

---

7. Clinical Manifestations

Hypercalcemia Symptoms

- Stones: nephrolithiasis
- Bones: fractures, bone pain
- Groans: constipation, pancreatitis
- Psychiatric overtones: depression, confusion
- Muscle weakness, fatigue

Hypocalcemia Symptoms

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- Perioral numbness
- Tetany
- Carpopedal spasm
- Chvostek/Trousseau signs
- Seizures

---

8. Laboratory Patterns (Exam-Critical)

Condition	Ca	Phos	PTH	Vitamin D
PHPT	↑	↓	↑	N/↓
SHPT (CKD)	↓/N	↑	↑	↓
SHPT (Vit D deficiency)	↓	↓	↑	↓
THPT	↑	↑	↑↑	N/↑
Hypoparathyroidism	↓	↑	↓	N

---

9. Imaging & Localization

When to Image

- **Only after biochemical diagnosis** of PHPT.
- Purpose: **localization**, not diagnosis.

Modalities

- **Ultrasound**: first-line; operator-dependent.
- **Sestamibi scan**: depends on oxyphil content.
- **4D-CT**: best for reoperative neck, ectopic glands.
- **MRI**: mediastinal or ectopic cases.

---

10. Parathyroid Ultrasound (High-Yield)

Normal Glands

- Usually **not visible** on US.

Adenoma Appearance

- Hypoechoic
- Homogeneous
- Well-circumscribed
- Peripheral vascular arc (feeding vessel)
- Posterior to thyroid

Hyperplasia

- Multiple enlarged glands
- Nodularity in long-standing SHPT

Limitations

- Poor visualization of:
  - Retropharyngeal
  - Retroesophageal
  - Mediastinal glands

---

11. Ultra-High-Yield Board Pearls

- Inferior glands = **3rd pouch**, descend with thymus → most variable.
- Superior glands = **4th pouch**, short descent → most constant.
- Most common ectopic site: **thymus**.
- Most common missed adenoma: **undescended inferior gland**.
- Intrathyroidal glands = 0.5–4%.

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- Oxyphil cells retain sestamibi → renal failure increases sensitivity.
- Severe hypomagnesemia → **low PTH despite low Ca**.
- PHPT: Ca ↑, PTH ↑ or "inappropriately normal."
- SHPT (CKD): phosphate ↑, vitamin D ↓, PTH ↑.
- THPT: autonomous PTH after transplant.
- Hypoparathyroidism most commonly **post-thyroidectomy**.
- Ultrasound cannot reliably see retroesophageal or mediastinal glands.
- 4D-CT is best for **reoperative** or **ectopic** cases.

---

12. ABSITE-Style One-Liners

- Inferior glands = most variable; superior = most constant.
- Thymus = most common ectopic site.
- PTH ↑ Ca, ↓ phosphate.
- Severe hypomagnesemia → ↓ PTH.
- PHPT = single adenoma 80–85%.
- SHPT (CKD) = high phosphate + low vitamin D.
- THPT = autonomous PTH after transplant.
- Hypoparathyroidism = most often surgical.
- Adenoma on US = hypoechoic, posterior, feeding vessel.
- 4D-CT = best for reoperative neck.

PRIMARY HYPERPARATHYROIDISM (Diagnosis & Surgical Management)

---

1. Overview & Epidemiology

Primary hyperparathyroidism (PHPT) is a disorder of **autonomous PTH secretion** from one or more parathyroid glands, leading to **hypercalcemia** and end-organ effects on bone, kidney, and neuromuscular systems. It is the **most common cause of hypercalcemia in the outpatient setting** and a core topic on endocrine boards and ABSITE.

Key epidemiologic features:

- Incidence increases with age; peak in **4th–6th decade**.
- **Women > men** (3–4:1).
- **80–85%** caused by a **single adenoma**.
- **15–20%** multiglandular disease (MGD): asymmetric hyperplasia or double adenomas.

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- <1% due to **parathyroid carcinoma**.
- Increasing detection due to routine chemistry panels → **asymptomatic PHPT is now predominant**.

---

2. Pathophysiology

PHPT results from **inappropriate PTH secretion** despite elevated serum calcium.

Mechanisms:

- PTH increases **bone resorption**, **renal Ca reabsorption**, **phosphate wasting**, and **calcitriol activation**.
- Hypercalcemia develops when PTH secretion becomes autonomous.
- Variants:
  - **Classic PHPT**: high Ca + high PTH.
  - **Normocalcemic PHPT**: normal Ca + high PTH (after excluding secondary causes).
  - **Normohormonal PHPT**: high Ca + normal PTH (inappropriately normal).

Genetic/inherited forms:

- MEN1
- MEN2A
- Hyperparathyroidism-jaw tumor syndrome (CDC73 mutation)
- Familial isolated hyperparathyroidism
- Familial hypocalciuric hypercalcemia (CaSR mutation; NOT surgical)

---

3. Clinical Presentation

Symptomatic PHPT

Symptoms arise from **hypercalcemia** or **PTH-mediated bone/kidney effects**.

- **Renal**: nephrolithiasis, nephrocalcinosis, polyuria, polydipsia.
- **Skeletal**: osteitis fibrosa cystica, fractures, bone pain.
- **GI**: constipation, nausea, pancreatitis, peptic ulcer disease.
- **Neuropsychiatric**: fatigue, depression, cognitive dysfunction.
- **Neuromuscular**: weakness, decreased muscle tone.

Asymptomatic PHPT

Most common presentation today:

- Mild hypercalcemia
- Osteopenia/osteoporosis
- Subclinical renal involvement

Variants

- **Normocalcemic PHPT**: elevated PTH with normal Ca; diagnosis of exclusion.

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- **Normohormonal PHPT**: normal PTH despite hypercalcemia; often MGD.

---

4. Laboratory Evaluation

Core labs

- **Serum calcium** (corrected or ionized)
- **PTH**
- **Phosphate**
- **Creatinine/eGFR**
- **25-OH vitamin D**
- **24-hour urine calcium**

Diagnostic patterns

- PHPT: **↑ Ca, ↑ PTH, ↓ phosphate**
- Normocalcemic PHPT: **N Ca, ↑ PTH**
- Normohormonal PHPT: **↑ Ca, N PTH**
- FHH: **↑ Ca, N/↑ PTH, ↓ urine Ca**

24-hour urine calcium

Critical for distinguishing PHPT vs FHH:

- PHPT: **normal or high urine Ca**
- FHH: **low urine Ca** (Ca/Cr clearance ratio <0.01)

---

5. Imaging & Localization

Imaging is NOT for diagnosis — only for preoperative localization.

First-line

- **Ultrasound**: operator-dependent; good for superficial glands.
- **Sestamibi scan**: depends on oxyphil content; may miss small or hyperplastic glands.

Advanced

- **4D-CT**: best for reoperative neck, ectopic glands, multigland disease.
- **MRI**: mediastinal or ectopic cases.
- **PET-CT (C-11 methionine or F-18 choline)**: emerging for difficult cases.

Localization pitfalls

- MGD often yields **negative or discordant imaging**.
- Intrathyroidal glands may mimic thyroid nodules.
- Ectopic glands require multimodal imaging.

---

6. Diagnosis

Diagnosis is **biochemical**, not radiologic.

Criteria:

- Elevated serum calcium **with** elevated or inappropriately normal PTH.
- Exclude secondary causes:
  - Vitamin D deficiency
  - CKD
  - Malabsorption
  - Medications (lithium, thiazides)

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Normocalcemic PHPT requires:

- Persistently normal Ca
- Elevated PTH
- Exclusion of secondary causes

---

7. Indications for Surgery (High-Yield)

Symptomatic PHPT

Surgery is **always indicated**.

Asymptomatic PHPT (Guideline-Based)

Surgery indicated if **any** of the following:

- Serum Ca >1 mg/dL above upper limit of normal
- T-score ≤ –2.5 at any site
- Vertebral fracture
- Creatinine clearance <60 mL/min
- Nephrolithiasis or nephrocalcinosis
- 24-hr urine Ca >400 mg/day
- Age <50 years
- Patient preference or inability to ensure follow-up

Special populations

- **Pregnancy**: surgery in 2nd trimester if symptomatic or severe hypercalcemia.
- **MEN syndromes**: tailored multigland approach.

---

8. Surgical Approaches

Focused (Minimally Invasive) Parathyroidectomy

Indications:

- Single adenoma
- Concordant localization studies
- No suspicion of MGD

Advantages:

- Smaller incision
- Shorter operative time
- Lower morbidity

Often combined with **intraoperative PTH monitoring (IOPTH)**.

Bilateral Neck Exploration (BNE)

Indications:

- Negative or discordant imaging
- Suspected MGD
- MEN syndromes
- Reoperative cases
- Normocalcemic or normohormonal PHPT with unclear localization

Principles:

- Identify all four glands
- Resect abnormal glands
- Preserve normal glands and vascular supply

Subtotal Parathyroidectomy

- Remove 3.5 glands
- Indicated for MGD, MEN1, renal hyperplasia (not PHPT but relevant)

Total Parathyroidectomy with Autotransplantation

- Reserved for select MGD cases
- Autotransplant into forearm

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9. Intraoperative PTH Monitoring (IOPTH)

Principle

PTH half-life ~3–4 minutes → rapid decline after adenoma removal.

Miami Criterion

- **>50% drop** from highest pre-excision value
- Measured at 10 minutes post-excision
- Indicates biochemical cure

When IOPTH is most useful

- Single adenoma with borderline imaging
- MGD suspicion
- Reoperative neck
- Normocalcemic PHPT
- Discordant imaging

Pitfalls

- Slow clearance in renal failure
- Double adenomas may cause false reassurance
- Manipulation of gland may transiently elevate PTH

10. Complications

Hypocalcemia

- Transient: common
- Permanent: rare
- Risk factors: MGD, extensive dissection, devascularization

Hungry Bone Syndrome

- Rapid bone remineralization after surgery
- Seen in severe PHPT or high bone turnover
- Requires close postoperative monitoring

Recurrent Laryngeal Nerve Injury

- Rare but serious
- Higher risk in reoperative cases

Persistent or Recurrent PHPT

- Persistent: hypercalcemia within 6 months
- Recurrent: hypercalcemia after 6 months of normocalcemia
- Causes: missed adenoma, ectopic gland, MGD

11. Postoperative Management

Calcium Monitoring

- Check Ca frequently in first 24–48 hours
- Watch for symptoms of hypocalcemia
- High-risk patients require closer monitoring

Vitamin D

- Optimize pre- and post-operatively to reduce hypocalcemia risk

Long-term Follow-Up

- Serum Ca and PTH
- Bone density
- Renal imaging if stones present pre-op

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12. High-Yield Surgical Pearls

- PHPT = **single adenoma in 80–85%**.
- Normohormonal PHPT often indicates **multigland disease**.
- FHH is **not surgical**; urine Ca is key.
- Imaging is for **localization**, not diagnosis.
- Negative imaging does **not** rule out PHPT.
- 4D-CT is best for **reoperative** or **ectopic** cases.
- IOPTH drop >50% = biochemical cure.
- Most common ectopic site for missed adenoma: **thymus**.
- Intrathyroidal glands = 0.5–4%.
- MEN1 → **multigland hyperplasia**, not single adenoma.
- Parathyroid carcinoma → **very high Ca + very high PTH + palpable mass**.
- Hungry bone syndrome occurs after removal of **high-turnover disease**.
- Persistent PHPT = missed gland; recurrent PHPT = regrowth or new disease.

---

13. ABSITE-Style One-Liners

- PHPT is the **most common cause of outpatient hypercalcemia**.
- Single adenoma = **85%**.
- FHH = **low urine Ca**.
- MEN1 = **multigland hyperplasia**.
- MEN2A = **single adenoma or hyperplasia**.
- Carcinoma = **PTH + Ca extremely high**.
- IOPTH half-life = **3–4 minutes**.
- Miami criterion = **>50% drop at 10 minutes**.
- Most common ectopic site = **thymus**.
- Negative imaging does **not** exclude PHPT.

RENAL HYPERPARATHYROIDISM (Secondary & Tertiary)

---

1. Overview & Epidemiology

Renal hyperparathyroidism encompasses **secondary hyperparathyroidism (SHPT)** due to chronic kidney disease (CKD) and **tertiary hyperparathyroidism (THPT)** when PTH secretion becomes autonomous after long-standing SHPT.

Key points:

- SHPT is **nearly universal** in advanced CKD.

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- THPT occurs in **10–30%** of patients after renal transplantation.
- SHPT is a **major driver of bone disease, vascular calcification, and cardiovascular morbidity** in CKD.
- Surgical management is common in **dialysis patients** and **post-transplant patients** with persistent hypercalcemia.

---

2. Pathophysiology of Secondary Hyperparathyroidism (SHPT)

Core Mechanisms in CKD

CKD disrupts mineral metabolism through several mechanisms:

- **Phosphate retention** → hyperphosphatemia → direct stimulation of PTH synthesis.
- **Decreased 1,25-OH vitamin D production** → ↓ Ca absorption → hypocalcemia → ↑ PTH.
- **Hypocalcemia** from impaired vitamin D activation and phosphate retention.
- **Downregulation of CaSR and VDR** in parathyroid cells → reduced sensitivity to Ca and vitamin D → ↑ PTH.
- **Skeletal resistance to PTH** due to decreased PTH receptor expression on osteoblasts.

Parathyroid Gland Morphology

- Early SHPT: **diffuse polyclonal hyperplasia**.
- Late SHPT: **nodular monoclonal hyperplasia**, often resistant to medical therapy.
- Nodular hyperplasia correlates with **poor response to calcimimetics and vitamin D analogs**.

Consequences

- High-turnover bone disease (osteitis fibrosa cystica).
- Vascular and soft-tissue calcification.
- Progressive gland enlargement → loss of feedback control.

---

3. Pathophysiology of Tertiary Hyperparathyroidism (THPT)

Definition

Autonomous PTH secretion after long-standing SHPT, typically **post-renal transplant**.

Mechanisms

- Chronic stimulation → monoclonal nodular hyperplasia → autonomous PTH secretion.
- Persistent hypercalcemia despite functioning graft.
- Glands fail to regress after correction of renal dysfunction.

Sara Yoslemi, MD.

Biochemical Pattern

- **High calcium**
- **High or very high PTH**
- **Low or normal phosphate**

---

4. Clinical Manifestations

Secondary HPT (CKD)

- Bone pain
- Pruritus
- Muscle weakness
- Fractures
- Calciphylaxis (rare but severe)
- Vascular calcification → cardiovascular morbidity
- Growth retardation in pediatric CKD

Tertiary HPT

- Hypercalcemia symptoms:
  - Fatigue
  - Constipation
  - Neurocognitive changes
  - Nephrolithiasis
- Persistent bone disease despite transplant
- Soft-tissue calcifications

---

5. Laboratory Evaluation

Secondary HPT (CKD)

- Calcium: **low or normal**
- Phosphate: **high**
- PTH: **high**
- Vitamin D: **low**
- Alkaline phosphatase: **elevated** (bone turnover)

Tertiary HPT

- Calcium: **high**
- Phosphate: **low or normal**
- PTH: **high or very high**

Key Distinctions

- SHPT = **hypocalcemia + hyperphosphatemia**
- THPT = **hypercalcemia + high PTH**
- PHPT = **hypercalcemia + high PTH + low phosphate**

---

6. Imaging & Localization

Purpose

Localization is **not required** for SHPT or THPT diagnosis but is useful for surgical planning.

Modalities

- **Ultrasound**: may show multiple enlarged glands; limited in CKD due to nodularity.
- **Sestamibi**: variable sensitivity; nodular hyperplasia may retain tracer.
- **4D-CT**: helpful in reoperative cases or ectopic glands.
- **MRI**: mediastinal or ectopic glands.

Patterns

- SHPT: **multiple enlarged glands**.
- THPT: often **one dominant gland** with others enlarged.

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7. Medical Management (Conceptual, Non-Directive)

Secondary HPT

- **Phosphate binders** to reduce hyperphosphatemia.
- **Vitamin D or VDR agonists** to suppress PTH.
- **Calcimimetics** to activate CaSR and reduce PTH secretion.
- **Dialysis optimization** to improve phosphate clearance.

Tertiary HPT

- Calcimimetics may reduce Ca and PTH.
- Persistent hypercalcemia or end-organ effects → surgical evaluation.

---

8. Indications for Surgery

Secondary HPT (CKD)

Surgery considered when:

- Severe, refractory SHPT despite medical therapy.
- PTH persistently very high with symptoms or complications.
- Calciphylaxis.
- Severe bone disease.
- Intractable pruritus.
- Soft-tissue or vascular calcifications.

Tertiary HPT

Surgery indicated when:

- Persistent hypercalcemia after transplant.
- Hypercalcemia causing renal graft dysfunction.
- Symptomatic hypercalcemia.
- Osteoporosis or fractures.
- Nephrolithiasis.
- Dominant gland enlargement with biochemical abnormalities.

---

9. Operative Strategies

Subtotal Parathyroidectomy (3.5 glands)

Most common approach for SHPT:

- Leaves a small remnant (~30–50 mg).
- Reduces recurrence risk while preserving function.

Total Parathyroidectomy with Autotransplantation

Indications:

- Severe SHPT with large glands.
- Reoperative cases.
- Patients unlikely to maintain follow-up.
- Autotransplant typically placed in **forearm** for easy access.

Focused Parathyroidectomy

More common in THPT when a **single dominant gland** is identified.

Cervical Thymectomy

Often performed with SHPT surgery due to:

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- High incidence of supernumerary glands in thymus.
- Prevention of persistent disease.

---

10. Intraoperative Considerations

Intraoperative PTH Monitoring

- Useful in THPT when a dominant gland is removed.
- Less reliable in SHPT due to multiple hyperfunctioning glands.

Gland Identification

- SHPT: all glands typically enlarged.
- THPT: one gland may be markedly enlarged.

Ectopic Glands

Common sites:

- Thymus
- Thyrothymic ligament
- Mediastinum
- Carotid sheath
- Retroesophageal space

---

11. Complications

Hypocalcemia

- Very common after SHPT surgery due to **hungry bone syndrome**.
- Requires close monitoring.

Recurrent Laryngeal Nerve Injury

- Risk increases with reoperative surgery.

Persistent or Recurrent HPT

- Persistent: missed gland or supernumerary gland.
- Recurrent: regrowth of remnant or autograft.

Hungry Bone Syndrome

- Rapid bone remineralization after removal of high-turnover glands.
- Seen in severe SHPT and THPT.

---

12. Postoperative Management

Calcium Monitoring

- Frequent monitoring in first 48–72 hours.
- High risk of hypocalcemia in SHPT.

Vitamin D Optimization

- Supports calcium homeostasis post-op.

Long-Term Follow-Up

- Serum Ca, PTH, phosphate.
- Bone density.
- Renal function.
- Graft function in transplant patients.

---

13. High-Yield Surgical Pearls

- SHPT = **low/normal Ca + high phosphate + high PTH**.
- THPT = **high Ca + high PTH** after transplant.
- Nodular hyperplasia = **poor response to medical therapy**.

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- SHPT glands: **all enlarged**; THPT: **one dominant gland**.
- Subtotal parathyroidectomy = **3.5 glands removed**.
- Total parathyroidectomy + autotransplant = for severe or recurrent disease.
- Thymectomy important due to **supernumerary glands**.
- Hungry bone syndrome common after SHPT surgery.
- Calciphylaxis is a severe complication of SHPT.
- Persistent disease often due to **ectopic or supernumerary glands**.

---

14. ABSITE-Style One-Liners

- SHPT is driven by **phosphate retention + ↓ vitamin D + ↓ CaSR/VDR**.
- THPT = autonomous PTH after transplant.
- SHPT labs: **low Ca, high phosphate, high PTH**.
- THPT labs: **high Ca, high PTH**.
- Subtotal parathyroidectomy = **3.5 glands**.
- Hungry bone syndrome = **post-op hypocalcemia**.
- Thymus = common site of supernumerary glands.
- Nodular hyperplasia = **monoclonal**.
- SHPT is **polyclonal → monoclonal** progression.
- Calcimimetics activate **CaSR**.

PARATHYROID CARCINOMA

---

1. Overview & Epidemiology

Parathyroid carcinoma is a **rare**, **aggressive**, and **high-morbidity** cause of primary hyperparathyroidism, accounting for **<0.5%** of all PHPT cases. Despite its rarity, it is **high-yield** for boards because:

- It presents with **extreme hypercalcemia** and **markedly elevated PTH**.
- It requires **en bloc surgical resection** at first operation for best outcomes.
- Recurrence is common and often biochemical before structural.
- Mortality is usually due to **uncontrolled hypercalcemia**, not tumor burden.

---

2. Etiology & Risk Factors

Sporadic Cases

Most cases are sporadic with no identifiable risk factor.

Genetic Associations

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- **CDC73 (HRPT2) mutation** → hyperparathyroidism-jaw tumor syndrome.
- Germline mutations increase risk of carcinoma.
- Loss of parafibromin expression is characteristic.

Radiation Exposure

Not clearly linked (unlike thyroid cancer).

Demographics

- Equal sex distribution (unlike benign PHPT).
- Occurs in younger patients compared to adenomas.

---

3. Pathophysiology

Parathyroid carcinoma causes **autonomous, excessive PTH secretion**, leading to:

- Severe hypercalcemia
- Bone resorption
- Renal dysfunction
- Soft-tissue calcification

Tumor behavior:

- Locally invasive
- High recurrence rate
- Hematogenous spread (lungs, liver, bone) less common than local recurrence

---

4. Clinical Presentation

Classic Triad (Boards Love This)

1. **Very high serum calcium** (often >14 mg/dL)
2. **Markedly elevated PTH** (often >3–10× upper limit)
3. **Palpable neck mass**

Symptoms

- Profound fatigue
- Bone pain, fractures
- Renal stones, nephrocalcinosis
- Severe constipation, pancreatitis
- Neurocognitive dysfunction
- Muscle weakness
- Dehydration and volume depletion

Red Flags Suggesting Carcinoma

- Palpable firm neck mass
- Vocal cord paralysis at presentation
- Calcium >14 mg/dL
- PTH extremely elevated
- Recurrent hypercalcemia after "successful" surgery
- Invasion into adjacent structures

---

5. Laboratory Findings

- **Calcium**: very high
- **PTH**: extremely high
- **Phosphate**: low
- **Alkaline phosphatase**: elevated (bone turnover)
- **Creatinine**: may be elevated due to hypercalcemia-induced nephropathy

Key Distinction

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Parathyroid carcinoma produces **much higher Ca and PTH** than benign PHPT.

---

6. Imaging & Localization

Ultrasound

- Large, lobulated, hypoechoic mass
- Irregular borders
- Possible invasion into thyroid or soft tissues

Sestamibi

- Intense uptake
- May show washout patterns

CT/MRI

- Evaluate local invasion
- Assess trachea, esophagus, RLN involvement

PET-CT

- Useful for recurrent/metastatic disease

Important

Imaging **cannot reliably distinguish** carcinoma from adenoma; clinical and biochemical features are key.

---

7. Diagnosis

Preoperative Diagnosis is Rare

Most cases are diagnosed **postoperatively** based on pathology.

Suspicious Features

- Severe hypercalcemia
- Very high PTH
- Palpable mass
- Vocal cord paralysis
- Invasion on imaging

Pathologic Criteria

- Capsular invasion
- Vascular invasion
- Perineural invasion
- Mitotic figures
- Fibrous bands
- Loss of parafibromin staining (CDC73 mutation)

Fine-Needle Aspiration

Contraindicated due to risk of tumor seeding.

---

8. Surgical Management

Principle

En bloc resection at first operation offers the best chance of cure.

Standard Operation

- **En bloc resection** of:
  - Parathyroid tumor
  - Ipsilateral thyroid lobe
  - Adjacent soft tissue
  - Involved structures (if safe)

Avoid

- Piecemeal excision
- Capsular rupture
- Tumor spillage
- FNA biopsy

Lymph Node Management

- Clinically positive nodes → **therapeutic central/lateral neck dissection**
- Prophylactic dissection **not recommended**

Reoperative Surgery

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Indicated for:

- Local recurrence
- Persistent hypercalcemia
- Symptomatic disease

Often challenging due to:

- Scar tissue
- Tumor adherence
- RLN involvement

---

9. Intraoperative Considerations

Intraoperative PTH

- May fall after tumor removal
- Not reliable for carcinoma due to:
  - Multigland involvement
  - Tumor secretion variability

Margins

- Aim for negative margins
- Avoid capsular disruption

RLN Management

- If tumor invades RLN:
  - Preserve if possible
  - Sacrifice only if necessary for oncologic control

---

10. Postoperative Management

Calcium Monitoring

- Risk of hungry bone syndrome
- Monitor Ca, Mg, phosphate closely

Long-Term Surveillance

- Serum Ca and PTH every 3–6 months
- Imaging for recurrence if biochemical markers rise
- Recurrence often biochemical before structural

Recurrence Patterns

- Local recurrence most common
- Distant metastases: lungs, liver, bone

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11. Adjuvant & Non-Surgical Therapies

Radiation

- Limited role
- May reduce local recurrence in select cases

Chemotherapy

- Generally ineffective

Targeted Therapy

- Investigational
- Limited evidence

Management of Hypercalcemia

- Hydration
- Agents that reduce serum calcium (conceptual, non-directive)
- Dialysis in severe cases

---

12. Prognosis

- 5-year survival: **~85%**
- 10-year survival: **~50–70%**
- Mortality usually due to **hypercalcemia**, not tumor burden

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- Recurrence rate: **40–60%**

---

13. High-Yield Surgical Pearls

- Parathyroid carcinoma = **very high Ca + very high PTH + palpable mass**.
- FNA is **contraindicated** due to seeding risk.
- Best chance of cure = **en bloc resection at first operation**.
- Ipsilateral thyroid lobectomy is part of standard en bloc resection.
- Local recurrence is common; surveillance is lifelong.
- Loss of parafibromin staining suggests **CDC73 mutation**.
- Hypercalcemia is the major cause of morbidity and mortality.
- Reoperative surgery is difficult due to scarring and invasion.
- Lymph node dissection is **therapeutic only**.
- Avoid capsular rupture at all costs.

---

14. ABSITE-Style One-Liners

- Parathyroid carcinoma = **<0.5%** of PHPT.
- Ca often **>14 mg/dL**; PTH **>3–10× normal**.
- Palpable neck mass strongly suggests carcinoma.
- FNA is **contraindicated**.
- Treatment = **en bloc resection**.
- Ipsilateral thyroid lobectomy included.
- Recurrence = **40–60%**.
- Mortality due to **hypercalcemia**, not metastasis.
- CDC73 mutation → carcinoma risk.
- Parafibromin loss = diagnostic clue.

PARATHYROIDECTOMY

Indications • Operative Techniques • Complications • Intraoperative PTH Monitoring • Autofluorescence • ICG

---

1. Overview

Parathyroidectomy is the definitive surgical treatment for **primary**, **secondary**, and **tertiary** hyperparathyroidism. Success depends on mastery of:

- Embryology
- Anatomy
- Ectopic locations
- Multigland disease patterns
- Localization strategies
- Intraoperative PTH monitoring
- Preservation of vascular supply
- Avoidance of RLN injury

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This chapter integrates all operative principles from your parathyroid chapters into a single surgical megadeck.

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2. Indications for Parathyroidectomy

Primary Hyperparathyroidism (PHPT)

Absolute indications:

- Symptomatic hypercalcemia
- Nephrolithiasis or nephrocalcinosis
- Osteoporosis or fragility fractures
- Hypercalcemic crisis

Guideline-based indications (asymptomatic):

- Serum Ca >1 mg/dL above upper limit
- T-score ≤ –2.5 at any site
- Vertebral fracture
- Creatinine clearance <60 mL/min
- 24-hr urine Ca >400 mg/day
- Age <50 years
- Patient preference

Secondary Hyperparathyroidism (SHPT)

Surgery considered when:

- Severe, refractory SHPT despite medical therapy
- Calciphylaxis
- Severe bone disease
- Intractable pruritus
- Soft-tissue or vascular calcifications
- PTH persistently very high with symptoms

Tertiary Hyperparathyroidism (THPT)

Indications:

- Persistent hypercalcemia after renal transplant
- Hypercalcemia causing graft dysfunction
- Symptomatic hypercalcemia
- Dominant gland enlargement
- Osteoporosis or fractures

---

3. Preoperative Evaluation

Biochemical Confirmation

- Ca, PTH, phosphate, creatinine, vitamin D
- 24-hr urine Ca (to exclude FHH)

Localization Studies

Localization is **not diagnostic**—only for surgical planning.

First-line:

- Ultrasound
- Sestamibi scan

Advanced:

- 4D-CT (best for reoperative neck, ectopic glands)
- MRI
- PET-CT (choline or methionine)

Voice Assessment

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- Preoperative laryngoscopy recommended in reoperative cases or voice symptoms.

---

4. Operative Approaches

A. Focused (Minimally Invasive) Parathyroidectomy

Ideal for:

- Single adenoma
- Concordant imaging
- No suspicion of multigland disease

Features:

- Small incision
- Directed dissection
- Often uses intraoperative PTH monitoring
- Lower morbidity

B. Bilateral Neck Exploration (BNE)

Indications:

- Negative or discordant imaging
- Multigland disease
- MEN syndromes
- Normocalcemic or normohormonal PHPT
- Reoperative cases

Principles:

- Identify all four glands
- Preserve normal glands and vascular supply
- Remove abnormal glands

C. Subtotal Parathyroidectomy (3.5 Glands)

Used for:

- Multigland hyperplasia
- MEN1
- Renal hyperparathyroidism

Remnant:

- ~30–50 mg of parathyroid tissue
- Usually left in situ with intact blood supply

D. Total Parathyroidectomy with Autotransplantation

Indications:

- Severe SHPT
- Reoperative disease
- Patients unlikely to maintain follow-up

Autotransplant:

- Typically into **forearm**
- Allows easy access for future removal

E. Cervical Thymectomy

Often performed in SHPT due to:

- High incidence of supernumerary glands
- Prevention of persistent disease

---

5. Operative Anatomy & Dissection Principles

Superior Parathyroids

- Posterior to thyroid
- Near cricothyroid junction
- Look in retroesophageal and paraesophageal spaces if not found

Inferior Parathyroids

- Variable location

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- Common sites: lower pole, thyrothymic ligament, thymus
- If not found → search thymus

Ectopic Glands

Common:

- Thymus
- Thyrothymic ligament
- Retroesophageal
- Mediastinum

Rare:

- Carotid sheath
- Intrathyroidal
- Vagus nerve

Vascular Preservation

- Preserve branches of inferior thyroid artery
- Avoid stripping capsule of normal glands

---

6. Intraoperative PTH Monitoring (IOPTH)

Principle

PTH half-life ~3–4 minutes → rapid decline after adenoma removal.

Miami Criterion

- **>50% drop** from highest pre-excision value
- Measured at **10 minutes** post-excision
- Indicates biochemical cure

When IOPTH is Most Useful

- Single adenoma with borderline imaging
- Multigland disease suspicion
- Reoperative neck
- Normocalcemic PHPT
- Discordant imaging

Pitfalls

- Slow clearance in renal failure
- Double adenomas may cause false reassurance
- Manipulation of gland may transiently elevate PTH

---

7. Autofluorescence & ICG Angiography

Autofluorescence (Near-Infrared)

Parathyroid tissue emits **intrinsic autofluorescence** under near-infrared light.

Advantages:

- Identifies glands without dissection
- Helps preserve vascular supply
- Useful in reoperative necks

Limitations:

- Cannot distinguish normal vs adenomatous glands
- Cannot confirm function

Indocyanine Green (ICG) Angiography

Used to assess **parathyroid perfusion**.

Advantages:

- Helps determine viability of preserved glands
- Guides decision for autotransplantation

Limitations:

- Requires specialized equipment

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- Perfusion does not always correlate with long-term function

8. Complications

Hypocalcemia

- Most common complication
- Transient vs permanent
- Risk factors: MGD, extensive dissection, devascularization

Hungry Bone Syndrome

- Seen after removal of high-turnover disease (SHPT, THPT)
- Requires close monitoring

Recurrent Laryngeal Nerve Injury

- Unilateral injury → hoarseness
- Bilateral injury → airway compromise

Hematoma

- Rare but life-threatening
- Requires immediate evacuation

Persistent or Recurrent Hyperparathyroidism

- Persistent: hypercalcemia within 6 months
- Recurrent: hypercalcemia after 6 months of normocalcemia

Causes:

- Missed gland
- Ectopic gland
- Supernumerary gland
- Regrowth of remnant or autograft

9. Postoperative Management

Calcium Monitoring

- Frequent checks in first 24–48 hours
- High-risk patients require closer monitoring

Vitamin D Optimization

- Supports calcium homeostasis

Long-Term Follow-Up

- Serum Ca and PTH
- Bone density
- Renal imaging if stones present pre-op

10. High-Yield Surgical Pearls

- PHPT = **single adenoma in 80–85%**.
- Negative imaging does **not** rule out PHPT.
- Imaging is for **localization**, not diagnosis.
- 4D-CT is best for **reoperative** or **ectopic** cases.
- Most common ectopic site: **thymus**.
- Intrathyroidal glands = 0.5–4%.
- Preserve vascular supply to normal glands.
- IOPTH drop >50% = biochemical cure.
- Subtotal parathyroidectomy = **3.5 glands removed**.

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- Total parathyroidectomy + autotransplant for severe SHPT.
- Hungry bone syndrome common after SHPT/THPT surgery.
- Avoid capsular rupture in suspected carcinoma.
- Reoperative surgery requires meticulous dissection and imaging.

---

11. ABSITE-Style One-Liners

- PHPT = **single adenoma**.
- SHPT = **low Ca, high phosphate, high PTH**.
- THPT = **high Ca, high PTH** after transplant.
- IOPTH half-life = **3–4 minutes**.
- Miami criterion = **>50% drop at 10 minutes**.
- Thymus = most common ectopic site.
- Subtotal parathyroidectomy = **3.5 glands**.
- Hungry bone syndrome = **post-op hypocalcemia**.
- Autofluorescence identifies glands; ICG assesses perfusion.
- Persistent disease = missed gland; recurrent = regrowth.

ATA 2025 Guideline for adult DTC

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1. Pathology, NIFTP, genetics (R1–R5)

R1 – Is NIFTP considered thyroid cancer?

Key idea:

- NIFTP = **noninvasive follicular thyroid neoplasm with papillary-like nuclear features**.
- Extremely low malignant potential; behaves like a borderline lesion.

Management:

- **Lobectomy is usually definitive.**
- No routine:
  - Completion thyroidectomy.
  - Lymph node dissection.
  - RAI.
- Follow-up is conservative; recurrence risk is extremely low.

Exam pearl: If final pathology is pure NIFTP with negative margins

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→ no RAI, no completion thyroidectomy.

R2–R5 – Genetic predisposition and counseling

R2 – Who should get germline genetic testing?

Offer germline testing in adults with DTC when:

- **Syndromic features**:
  - PTEN hamartoma syndrome, DICER1, FAP, Carney complex, etc.
- **Strong family history**:
  - Multiple first-degree relatives with non-medullary thyroid cancer.
- **Early onset** or multiple primary tumors.

R3 – Non-syndromic FNMTC

- Consider germline testing when:
  - ≥3 affected first-degree relatives, or
  - Early onset/aggressive disease.
- Not mandatory for every small family cluster.

R4 – Screening relatives

- Neck US screening can be considered in first-degree relatives in well-defined FNMTC families.
- Balance early detection vs overdiagnosis and anxiety.

R5 – Germline testing after somatic findings

- If tumor sequencing reveals variants suggestive of germline predisposition (e.g., PTEN, TP53, mismatch repair), **offer confirmatory germline testing** with genetics input.

Clinician note: Genetics is **selective**, not universal. On exams, look for "multiple relatives + early onset" or "syndromic features" as triggers.

---

2. Initial management, surgery, active surveillance (R6–R21)

R6 – Surgical experience and complications

- Higher-volume thyroid surgeons → **lower RLN injury, hypocalcemia, hematoma, reoperation**.
- For complex cases (re-operations, extensive nodal disease, invasive tumors), guidelines favor experienced surgeons.

Exam pearl: If question contrasts high- vs low-volume surgeon, guidelines clearly favor high-volume for thyroidectomy.

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R7–R10 – Preoperative workup

R7 – Preoperative imaging and labs

- **Neck ultrasound**:
  - Mandatory for thyroid and cervical nodes.
- **CT/MRI**:
  - Suspected gross ETE, tracheal/esophageal invasion, mediastinal nodes.
  - Use contrast if needed; iodine load is manageable with planning.
- **Labs**:
  - TSH, calcium, vitamin D, baseline Tg (optional but useful).

R8 – When CT/MRI/FDG-PET pre-op?

- CT/MRI:
  - Large tumors, suspected invasion, bulky nodes, re-operative neck.
- FDG-PET:
  - Rarely pre-op; more for aggressive histology or suspected distant disease.

R9 – Preoperative Tg

- Tg can be measured as a **baseline**, but:
  - Does **not** replace imaging.
  - Not required in all patients.

R10 – Preoperative somatic genomic testing

- Routine pre-op somatic testing **not recommended** just to decide lobectomy vs total thyroidectomy.
- May help in:
  - Indeterminate nodules.
  - Suspected aggressive variants.
  - Planning systemic therapy later.

Clinician note: For ABSITE/ESE, pre-op workup = US for all, CT/MRI for invasive disease, Tg optional, somatic testing not routine.

R11–R14 – Active surveillance and percutaneous ablation

R11 – Who is eligible for active surveillance or ablation?

- **Active surveillance**:
  - Papillary microcarcinoma ≤1 cm.
  - No ETE, no clinically evident nodes, no high-risk features.
  - Patient reliable and comfortable with surveillance.
- **Percutaneous ablation** (e.g., RFA, ethanol):

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    - Small, localized lesions.
    - Surgery high-risk or refused.
    - Also used for small recurrent nodes in selected cases.

R12 – Active surveillance protocol

- Neck US and clinical exam:
    - Typically at 6–12 months initially, then spaced if stable.
- Document:
    - Tumor size, location, proximity to RLN/trachea.
- Switch to surgery if:
    - Significant growth.
    - New nodes.
    - Symptoms or invasion.

R13 – Tg/TgAb during active surveillance

- Tg/TgAb can be followed, but:
    - **Structural changes on imaging drive decisions**.
    - Tg alone should not trigger surgery in stable microPTC.

R14 – Indications to convert to surgery

- Growth beyond pre-defined thresholds (e.g., >3 mm).
- New nodal disease.
- Local invasion or symptoms.
- Patient preference or anxiety.

Exam pearl: MicroPTC with no high-risk features → active surveillance is guideline-endorsed; know the triggers to operate.

R15–R21 – Extent of surgery, central neck, voice, parathyroids

R15 – Optimal operative approach

- **Lobectomy**:
    - Intrathyroidal, low-risk tumors (e.g., ≤4 cm, no ETE, no nodes, no high-risk histology).
- **Total thyroidectomy**:
    - Larger tumors.
    - ETE.
    - Nodal disease.
    - RAI planned.
    - Aggressive histology.

R16 – Completion thyroidectomy

- Consider when:
    - Final pathology shows higher-risk features than expected.
    - RAI is indicated and total thyroidectomy is preferred.
- Not mandatory for all small, low-risk tumors initially treated with lobectomy.

R17–R18 – Thyroglossal duct carcinoma

- **R17:** Sistrunk procedure is primary.

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- **R18:** Completion thyroidectomy considered if:
  - Concomitant thyroid carcinoma.
  - High-risk features.
  - Need for RAI.

R19 – Prophylactic central neck dissection

- **Not routine** for all PTC.
- Consider in:
  - Large tumors.
  - ETE.
  - Clinically suspicious nodes.
  - High-risk histology.
- Must be done by experienced surgeon.

R20 – Therapeutic central and lateral neck dissection

- Compartment-oriented dissection for **clinically involved** nodes.
- Avoid "berry picking" (removing only individual nodes).

R21 – Perioperative voice and parathyroid issues

- Pre-op counseling about:
  - Voice changes.
  - Hypocalcemia.
- Intra-op:
  - Preserve RLN and parathyroids.
  - Use nerve monitoring as appropriate.

Clinician note: On exams, prophylactic central neck dissection is **selective**, not universal; therapeutic dissection is standard for clinically involved nodes.

---

3. Voice, RLN, parathyroids, pathology, risk (R22–R30)

R22–R24 – RLN and parathyroids

R22 – Pre-op laryngeal exam

- Recommended when:
  - Prior neck surgery.
  - Voice changes.
  - Large or invasive tumors.
  - Planned re-operation.

R23 – Intraoperative RLN assessment

- Visual identification is standard.
- Nerve monitoring:
  - Helps reduce risk.
  - Guides staged surgery decisions (e.g., stopping after one side if loss of signal).

R24 – Parathyroid management

- Preserve in situ with intact blood supply.
- Autotransplant devascularized glands (e.g., into sternocleidomastoid).
- Monitor calcium and treat hypocalcemia promptly.

Common complications:

- Transient hypocalcemia.

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- Permanent hypoparathyroidism.
- RLN palsy (unilateral or bilateral).

R25–R27 – Drains, voice changes, pathology

R25 – Drains after thyroidectomy

- Routine drains **not required**.
- Consider in:
  - Large dead space.
  - High bleeding risk.
  - Extensive dissection.

R26 – Post-op voice changes

- Evaluate with laryngoscopy if persistent.
- Early referral to:
  - Voice therapy.
  - Laryngology.
- Consider medialization procedures if permanent unilateral palsy.

R27 – Histopathologic evaluation

- Report:
  - Tumor size.
  - Histologic subtype.
  - ETE (minimal vs gross).
  - Margins.
  - Lymphovascular invasion.
  - Nodal status and extranodal extension.

R28–R30 – Risk stratification and early response

R28 – Risk of recurrence assessment

- Use **ATA risk categories**:
  - Low.
  - Low-intermediate.
  - High-intermediate.
  - High.
- Factors:
  - Tumor size.
  - ETE.
  - Nodal burden (number, size, extranodal extension).
  - Histology.

R29 – Assessing response to surgery

- Combine:
  - Tg, TgAb.
  - Imaging (US ± CT/MRI/RAI scans).
- Classify:
  - Excellent response.
  - Indeterminate.
  - Biochemical incomplete.
  - Structural incomplete.

R30 – Tg measurement after surgery

- Measure Tg (and TgAb) after surgery and periodically thereafter.
- Timing depends on:
  - RAI use.
  - Risk category.
  - Clinical context.

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Exam pearl: Dynamic risk stratification (R29–R30, R51) is central—response category modifies initial ATA risk.

---

4. Imaging & RAI in primary management (R31–R44)

R31 – Role of US, CT, MRI, FDG-PET after resection

"Ultrasound to evaluate the thyroid bed and central and lateral cervical lymph node compartments is the preferred method of imaging surveillance for most DTC."

Key points:

- First US at **6–12 months** after completion of initial therapy.
- Frequency thereafter based on risk and response.
- Suspicious nodes:
  - <8–10 mm → can be observed unless growth or threat to vital structures.
  - ≥8–10 mm → FNA + Tg washout if result will change management.
- Rising Tg with negative/low-yield US:
  - CT/MRI of lungs and bone.
  - FDG-PET/CT in RAIR, OTC, PDTC, or Tg-positive/scan-negative.

R32 – RAI after thyroidectomy (core exam topic)

"Remnant ablation is not recommended routinely after total thyroidectomy for patients with ATA low-risk DTC."

Risk-based RAI strategy:

- **ATA low-risk**
  - **No routine RAI**.
  - If used (select cases): **1.1–1.85 GBq (30–50 mCi)** for remnant ablation only.
- **ATA intermediate-risk (low-intermediate & high-intermediate)**
  - **RAI adjuvant therapy may be considered**.
  - Typical dose: **1.1–3.7 GBq (30–100 mCi)**.
- **ATA high-risk**
  - **RAI adjuvant therapy recommended routinely**.
  - Dose: **3.7–5.55 GBq (100–150 mCi)**.
- **Distant metastases at diagnosis**
  - RAI routinely recommended after total thyroidectomy.

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- Dose: **3.7–7.4 GBq (100–200 mCi)** or dosimetry.

Table 10 summary:

- Low risk: 1.1–1.85 GBq (30–50 mCi) if used.
- Intermediate: 1.1–3.7 GBq (30–100 mCi).
- High: 3.7–5.55 GBq (100–150 mCi).
- Distant mets: 3.7–7.4 GBq (100–200 mCi), consider dosimetry.

R33 – RAI for oncocytic (Hürthle cell) carcinoma (OTC)

- Data conflicting; some series show benefit, others do not.
- If RAI not given empirically, consider **diagnostic WBS** to assess iodine avidity.
- Improved Tg-based monitoring may be a rationale for RAI in selected higher-risk OTC.

R34 – Preparation for RAI

"In patients with DTC in whom RAI remnant ablation or adjuvant therapy is planned, preparation with rhTSH stimulation is preferred over thyroid hormone withdrawal."

Key points:

- **Preferred:** rhTSH for remnant ablation/adjuvant therapy.
- **TSH goal:** >30 mIU/L before RAI.
- If withdrawal:
  - Stop LT4 for 3–4 weeks.
  - Consider LT3 bridge for first 2 weeks; stop LT3 ≥2 weeks before RAI.
- In distant mets:
  - Either withdrawal or rhTSH acceptable.

Exam pearl: rhTSH is preferred for remnant ablation/adjuvant therapy; withdrawal is still acceptable, especially in metastatic disease.

R35–R38 – Low-iodine diet, diagnostic and post-therapy WBS, SPECT-CT

R35 – Low-iodine diet

- Short low-iodine diet (≈1–2 weeks) before RAI to optimize uptake.
- Avoid iodized salt, dairy, seafood, kelp, some processed foods.

R36 – Diagnostic WBS

- Use selectively; not mandatory in all low-risk patients.
- More useful in:
  - Higher-risk patients.
  - Planning RAI therapy.
  - Evaluating suspected recurrence.

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R37 – Post-therapy WBS

- Recommended after therapeutic RAI to:
  - Document distribution.
  - Detect unsuspected disease.

R38 – SPECT-CT

- Consider SPECT-CT with WBS to:
  - Better localize uptake.
  - Distinguish physiologic vs pathologic foci.

R39–R44 – Safety, side effects, EBRT

R39 – Radiation safety counseling

- Educate on:
  - Limiting close contact with others (especially children, pregnant women).
  - Hygiene (flush twice, handwashing).
  - Sleeping arrangements and work restrictions for a few days.

R40 – Salivary/lacrimal side effects

- Risks:
  - Sialadenitis.
  - Xerostomia.
  - Taste changes.
  - Dry eyes.
- Mitigation:
  - Hydration.
  - Timed sour candies (not too early).
  - Salivary gland massage.
  - Eye lubrication.

R41 – Second primary malignancy

- Small but real increased risk with higher cumulative RAI doses.
- Counsel especially when considering repeated high-dose RAI.

R42 – Other testing in RAI patients

- Monitor:
  - CBC (marrow suppression).
  - Renal function.
  - Liver function as needed.

R43 – RAI and pregnancy, nursing, gonadal function

- **Contraindicated in pregnancy and breastfeeding.**
- Counsel on:
  - Temporary gonadal dysfunction.
  - Fertility considerations.
  - Timing of conception after RAI (often ≥6–12 months).

R44 – Role of radiotherapy ± chemotherapy

- EBRT (IMRT preferred) for:

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    - Unresectable gross residual disease.
    - Non-RAI-avid locoregional disease.
    - Painful or threatening lesions (e.g., airway, spine).
- Chemotherapy:
    - Limited role; mainly in selected advanced cases or combined with RT.

Clinician note: For exams, EBRT is **not** first-line for typical low-risk DTC; it's for unresectable, non-RAI-avid, or recurrent locoregional disease.

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5. Long-term management, TSH, Tg, imaging (R45–R51)

R45–R46 – TSH suppression

R45 – Degree of TSH suppression

- **High-risk / active disease:**
    - TSH suppression below reference range (often <0.1 mIU/L).
- **Intermediate-risk:**
    - Moderate suppression (e.g., 0.1–0.5).
- **Low-risk, excellent response:**
    - TSH can be maintained in low-normal range.

R46 – Duration of suppression

- Maintain stronger suppression longer in:
    - High-risk patients.
    - Incomplete response.
- Relax suppression over time in:
    - Low-risk patients with excellent response.

Adverse effects of long-term suppression:

- Atrial fibrillation.
- Bone loss (especially in postmenopausal women).
- Symptoms of subclinical hyperthyroidism.

R47–R51 – Tg, de-escalation, imaging, dynamic risk

R47 – Role of Tg in follow-up

- Tg (and TgAb) is central to follow-up after total thyroidectomy ± RAI.
- Use:
    - On TSH suppression.
    - With TSH stimulation in selected cases.

R48 – De-escalation in low-risk DTC

- In ATA low-risk with excellent response (undetectable Tg, negative US):
    - **Monitoring can be spaced out and eventually de-escalated**.
    - Long-term intensive imaging not required.

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R49–R50 – Imaging during follow-up

- Neck US is first-line.
- Diagnostic WBS and SPECT-CT:
  - Reserved for higher-risk or suspected recurrence.
- FDG-PET/CT:
  - For suspected RAIR disease.
  - Tg-positive/scan-negative cases.

R51 – Ongoing risk stratification (response to therapy)

- Dynamic risk stratification:
  - Excellent vs incomplete vs indeterminate response.
- Guides:
  - Intensity of surveillance.
  - TSH suppression.
  - Need for further therapy.

Exam pearl: Dynamic risk stratification can "downstage" many initially intermediate-risk patients after an excellent response.

---

6. Locoregional recurrence, RAI dosing for mets, RAIR definition (R52–R60)

R52–R54 – Locoregional residual/recurrent disease

R52 – Treatment of locoregional residual/recurrent DTC

- Options:
  - Surgery (preferred when feasible).
  - RAI (if iodine-avid).
  - EBRT (IMRT).
  - Ablation (RFA, ethanol).
- Multidisciplinary decision based on:
  - Site.
  - Volume.
  - Prior treatments.
  - Comorbidities.

R53 – RAI for isolated cervical nodes

- RAI **alone** is usually insufficient for bulky nodal disease.
- Surgery is preferred; RAI may be adjunctive.

R54 – EBRT for isolated cervical nodes

- Consider EBRT when:
  - Surgery not feasible.
  - Non-RAI-avid disease.
  - Recurrent disease in previously operated fields.

R55–R57 – RAI dosing strategies for mets

R55 – RAI dosing for locoregional/distant mets

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- Empiric vs dosimetry-based dosing.
- Typical empiric doses: **3.7–7.4 GBq (100–200 mCi)**.
- Consider dosimetry in:
  - Older patients.
  - Diffuse lung mets.
  - Renal impairment.

R56 – RAI dosing for pulmonary mets

- Similar range (3.7–7.4 GBq).
- Be cautious with diffuse lung mets:
  - Risk of pulmonary fibrosis.
  - Dosimetry often preferred.

R57 – RAI dosing for bone mets

- Higher doses often needed (3.7–7.4 GBq).
- Combine with:
  - Surgery.
  - EBRT (IMRT or SBRT).
  - Cementoplasty or other local measures.

R58–R60 – Empiric RAI, RAIR classification, observation

R58 – Empiric RAI in Tg-positive, scan-negative

- Empiric RAI may be considered in Tg-positive, diagnostic scan-negative patients.
- Benefit uncertain; weigh:
  - Potential detection/treatment vs
  - Radiation risks and second malignancy risk.

R59 – How is RAIR DTC classified?

- RAIR if:
  - No uptake in known lesions.
  - Loss of uptake in previously avid lesions.
  - Progression despite adequate RAI.
  - Mixed pattern with some non-avid lesions.

R60 – Which metastatic patients can be observed?

- Selected patients with:
  - Small-volume, slowly progressive disease.
  - Minimal symptoms.
- Can be followed with imaging and Tg without immediate systemic therapy.

Exam pearl: RAIR is a functional definition—loss of iodine avidity or progression despite adequate RAI.

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7. Systemic therapy for RAIR DTC (R61–R76)

R61–R63 – Choosing therapy and timing

R61 – Choosing best therapy in RAIR DTC

Sam Mosleri, MD

- First ask: **Is there an actionable driver?**
  - RET, NTRK, ALK, BRAFV600E, others.
- If yes → gene-specific targeted therapy.
- If no → MKIs (lenvatinib, sorafenib).

R62 – First-line therapy without actionable driver

"For patients with progressive RAIR DTC without an actionable biomarker-linked FDA-approved first-line therapy, MKI therapy with either lenvatinib or sorafenib is recommended. In most cases, lenvatinib is the preferred first-line MKI."

- Lenvatinib or sorafenib; **lenvatinib preferred** based on:
  - Higher response rate.
  - Longer PFS.

R63 – Timing of MKI initiation

"Lenvatinib or other therapy should be initiated without delay in patients with symptomatic RAIR DTC for whom local therapy, such as radiation or surgery, is not appropriate."

- Start lenvatinib (or other therapy) **without delay** in:
  - Symptomatic RAIR DTC where local therapy not appropriate.
- Asymptomatic but progressive:
  - If efficacy prioritized → earlier initiation reasonable.
  - If QoL prioritized → delay and monitor.

Clinician note: Shared decision-making is emphasized—some patients prioritize QoL over maximal PFS.

R64–R66 – Lenvatinib dosing, AE management, second line

R64 – Best starting dose of lenvatinib

"For most patients with progressive RAI-refractory DTC initiating lenvatinib, 24 mg once daily is the recommended starting dose; a lower starting dose may be indicated in selected patients."

- Standard: **24 mg once daily**.
- Lower starting dose (e.g., 14–18 mg) in:
  - Severe renal impairment (CrCl <30 mL/min).
  - Child-Pugh C liver disease.
  - Frail patients or difficult hypertension.
- Dose holds and reductions are key strategies.

R65 – Managing VEGFR MKI adverse events

Sam Mosleri, MD

"Prevention, amelioration, and timely management of adverse events are required for patients treated with MKIs. Patients initiating MKI therapy should be evaluated at baseline and no less often than every 2 weeks for the first 2 months of treatment…"

- Baseline and frequent follow-up:
  - Every 2 weeks for first 2 months, then q1–2 months.
- Hypertension:
  - Very common; treat aggressively (CCB, ACEi, ARB, etc.).
  - If MKI held, adjust antihypertensives as drug clears.
- HFS:
  - Prophylactic skin care, urea creams, podiatry.
- Diarrhea, stomatitis, weight loss:
  - Diet modification, antidiarrheals, nutrition support.
- Monitor:
  - TSH, free T4.
  - Electrolytes, proteinuria.
  - QTc, cardiac function.
- Rare but serious:
  - GI perforation.
  - Fistula.
  - Bleeding.
  - Thromboembolism.
  - RPLS.

R66 – Preferred second-line therapy

- **Cabozantinib** is recommended second-line for RAIR DTC without actionable driver after progression or intolerance to prior MKI.
- Dose (cabozantinib tablets, Cabometyx): typically, 60 mg daily, with reductions as needed.

Exam pearl: Lenvatinib first-line, cabozantinib second-line in RAIR DTC without actionable driver.

R67–R71 – Gene-specific targeted therapy

R67 – NTRK fusion-positive RAIR DTC

- First-line: **TRK inhibitor** (e.g., larotrectinib, entrectinib).
- High response rates; often well tolerated.

R68 – RET fusion-positive RAIR DTC

- First-line: **RET inhibitor** (e.g., selpercatinib, pralsetinib).
- High response rates; monitor for:
  - Hypertension.

Sam Mosleh, MD

- Liver enzyme elevations.
- QT prolongation.

R69 – ALK fusion-positive RAIR DTC

- First-line: **ALK inhibitor** (e.g., alectinib, crizotinib).
- Monitor for:
  - Liver toxicity.
  - Pneumonitis.
  - Bradycardia.

R70 – BRAFV600E mutation-positive RAIR DTC

- First-line: BRAF-directed therapy (e.g., dabrafenib ± MEK inhibitor).
- Adverse effects:
  - Fever.
  - Skin toxicity.
  - Arthralgias.
  - Secondary skin cancers.

R71 – Other actionable targets

- For other actionable alterations (e.g., ROS1, MET, others), use corresponding targeted agents when available.
- Often in the context of clinical trials.

Clinician note: For boards, know that **driver-specific therapy is preferred first-line** when an FDA-approved agent exists.

R72–R76 – Progression on targeted therapy, immunotherapy, redifferentiation, chemo, oligometastatic disease

R72 – Progression on gene-specific therapy

- Consider:
  - Switching to another targeted agent (if available).
  - MKI therapy (lenvatinib, cabozantinib).
  - Local therapies for oligoprogression (SBRT, surgery).

R73 – Role of immunotherapy

- Immunotherapy (e.g., PD-1 inhibitors) has a limited but emerging role.
- Consider in:
  - High TMB.
  - MSI-H.
  - Clinical trials.

R74 – Redifferentiation therapy

- Use kinase inhibitors (e.g., MEK, BRAF inhibitors) to restore iodine avidity in some RAIR tumors, followed by RAI.
- Particularly relevant in BRAFV600E-mutant tumors.

R75 – Cytotoxic chemotherapy

- Limited role; consider in:
  - Heavily pretreated patients.
  - No other options.

Sam Moslemi, MD

- Agents: doxorubicin, taxanes (rarely used now).

R76 – Oligometastatic RAIR DTC

- Local therapies (surgery, SBRT, ablation) for limited metastases to:
  - Control disease.
  - Delay systemic therapy.

Exam pearl: Systemic therapy ladder = driver-specific → MKI (lenvatinib) → cabozantinib → other MKIs/chemo/trials.

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8. Site-specific issues, bone/brain, trials, pregnancy, survivorship (R77–R84)

R77–R80 – Bone, brain, clinical trials

R77 – Site-specific symptomatic RAIR DTC

- Use local therapies for symptomatic lesions:
  - Surgery.
  - EBRT (IMRT, SBRT).
  - Ablation.
  - Embolization.
- Examples:
  - Airway compression.
  - Esophageal invasion.
  - Painful spine lesions.

R78 – Bone-directed agents

- Consider:
  - Bisphosphonates (e.g., zoledronic acid).
  - Denosumab.
- Goal:
  - Reduce skeletal-related events (fractures, spinal cord compression).

R79 – Brain metastases

- Treat with:
  - Surgery.
  - Stereotactic radiosurgery (SRS).
  - Whole-brain RT (WBRT) when needed.
- Systemic therapy:
  - Tailored to driver status and RAIR status.
  - Some targeted agents have CNS activity (e.g., certain RET, NTRK, ALK inhibitors).

R80 – Clinical trials

- Strongly consider clinical trial enrollment for RAIR DTC, especially after standard options.

R81–R84 – Pregnancy, survivorship, financial toxicity, psychosocial issues

R81 – Managing pregnant patients with DTC

- Delay RAI until after pregnancy and breastfeeding.
- Surgery in pregnancy:
  - Only when necessary (e.g., rapidly growing or compressive tumors).

Sam Moslemi, MD

- Ideally in 2nd trimester.
- TSH management:
  - Tailored to risk; avoid overtreatment.

R82 – Long-term survivorship concerns

- Address:
  - Hypothyroidism management.
  - Hypocalcemia.
  - RAI late effects (salivary, lacrimal, second malignancies).
  - Cardiovascular risk with long-term TSH suppression.
  - Bone health (especially in postmenopausal women).

R83 – Financial hardship ("financial toxicity")

- Recognize and address financial burden of:
  - Surgery.
  - RAI.
  - Long-term hormone therapy.
  - Targeted therapies and MKIs.
- Connect patients with:
  - Social work.
  - Financial counseling.
  - Assistance programs.

R84 – Psychosocial concerns

- Screen for:
  - Anxiety.
  - Depression.
  - Fear of recurrence.
- Encourage:
  - Support groups.
  - Counseling.
  - Survivorship programs.

ATA 2025 DTC ONE-PAGER

Risk Stratification → Surgery → RAI → Follow-up

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1) ATA RISK STRATIFICATION (POST-OP)

Used to decide **extent of surgery**, **RAI**, **TSH suppression**, and **follow-up intensity**.

ATA LOW RISK

- Intrathyroidal PTC or FTC
- No gross ETE
- ≤5 small nodes (<0.2 cm)
- No aggressive histology
- No vascular invasion
- No distant mets

Clinical meaning: Excellent prognosis; avoid overtreatment.

ATA LOW-INTERMEDIATE RISK

- Microscopic ETE
- 1–5 metastatic nodes 0.2–1 cm
- Limited vascular invasion
- Non-aggressive histology

Clinical meaning: Consider RAI selectively.

Sam Mosleh, MD

ATA HIGH-INTERMEDIATE RISK

- 5 metastatic nodes
- Any node ≥1 cm
- Extranodal extension
- Aggressive histology (tall cell, hobnail, diffuse sclerosing)
- Significant vascular invasion

Clinical meaning: RAI more strongly considered.

ATA HIGH RISK

- Gross ETE
- Incomplete resection
- Distant metastases
- Very high Tg
- Large/bulky nodal disease

Clinical meaning: RAI routinely recommended; intensive follow-up.

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2) SURGERY DECISION MAP

A. LOBECTOMY

Indications:

- Low-risk intrathyroidal tumors ≤4 cm
- No ETE
- No nodal disease
- No aggressive histology
- Patient preference or comorbidity limiting total thyroidectomy

Advantages: Lower complication risk (RLN, hypocalcemia).

B. TOTAL THYROIDECTOMY

Indications:

- Tumor >4 cm
- ETE (gross or microscopic)
- Clinically positive nodes
- Aggressive histology
- RAI planned
- Bilateral disease

C. COMPLETION THYROIDECTOMY

Indications:

- Post-lobectomy pathology reveals:
  - High-intermediate or high-risk features
  - Aggressive histology
  - Vascular invasion
  - Nodal metastases
  - RAI indicated

D. CENTRAL NECK DISSECTION

- **Therapeutic**: For clinically involved nodes (standard of care).
- **Prophylactic**: *Not routine.* Consider only in:
  - Large tumors
  - ETE
  - High-risk histology
  - Experienced surgeon

---

3) RAI DECISION MAP (R32–R44)

A. WHEN TO USE RAI?

Sam Moslemi, MD.

Risk Group	RAI Recommendation	Typical Dose
Low Risk	**Not routine**	1.1–1.85 GBq (30–50 mCi) *if used*
Low-Intermediate	**Consider**	1.1–3.7 GBq (30–100 mCi)
High-Intermediate	**Consider / often recommended**	1.1–3.7 GBq (30–100 mCi)
High Risk	**Routine**	3.7–5.55 GBq (100–150 mCi)
Distant Mets	**Routine**	3.7–7.4 GBq (100–200 mCi) or dosimetry

Guideline anchor:
"Remnant ablation is not recommended routinely after total thyroidectomy for patients with ATA low-risk DTC."

B. RAI GOALS

- **Remnant ablation:** Remove normal thyroid tissue to improve Tg monitoring.
- **Adjuvant therapy:** Reduce recurrence risk.
- **Treatment of known disease:** Treat iodine-avid metastases.

C. PREPARATION FOR RAI (R34)

- **Preferred:** rhTSH stimulation
- **Alternative:** Thyroid hormone withdrawal
- **TSH goal:** >30 mIU/L
- **Low-iodine diet:** 1–2 weeks pre-RAI

D. WHEN RAI IS NOT EFFECTIVE

- BRAFV600E + TERT promoter mutations → poor iodine avidity
- Loss of uptake on scans
- Progression despite adequate RAI

Sam Moslemi, MD

This defines **RAI-refractory (RAIR)** disease.

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4) FOLLOW-UP & IMAGING (R31, R45–R51)

A. ULTRASOUND

- First US: **6–12 months** post-op
- Then based on risk + response
- Nodes ≥8–10 mm → FNA + Tg washout
- Nodes <8 mm → observe unless growing or threatening structures

Guideline anchor:
"Ultrasound…is the preferred method of imaging surveillance for most DTC."

B. Tg & TgAb

- Tg is central after total thyroidectomy ± RAI
- Rising Tg with negative US → CT/MRI chest, bone imaging
- Consider FDG-PET in RAIR or aggressive histology

C. TSH SUPPRESSION

- **High risk / active disease:** TSH <0.1
- **Intermediate:** 0.1–0.5
- **Low risk, excellent response:** Low-normal range

Risks: AFib, osteoporosis (especially postmenopausal women).

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5) WHEN TO USE EBRT, SBRT, OR ABLATION

EBRT (IMRT)

Indications:

- Unresectable gross residual disease
- Non-RAI-avid locoregional recurrence
- Painful or threatening lesions (airway, esophagus, spine)

SBRT

- Oligometastatic disease (bone, lung, brain)
- Pain control
- Local progression control

Percutaneous Ablation (RFA, ethanol)

- Small recurrent nodes
- Patients unfit for surgery
- MicroPTC in selected cases

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6) SYSTEMIC THERAPY (RAIR DISEASE)

First-line if actionable mutation:

- **RET fusion:** Selpercatinib / Pralsetinib
- **NTRK fusion:** Larotrectinib / Entrectinib
- **ALK fusion:** Alectinib / Crizotinib
- **BRAFV600E:** Dabrafenib ± Trametinib

Sam Moslemi, MD.

First-line if NO actionable mutation (R62):

- **Lenvatinib** (preferred)
- Sorafenib

Common adverse effects:
Hypertension, diarrhea, weight loss, HFS, proteinuria, QT prolongation.

Second-line (R66):

- **Cabozantinib**

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7) DYNAMIC RISK STRATIFICATION (R51)

Used at 6–24 months post-treatment.

Response Category	Definition	Management
Excellent	Undetectable Tg, negative imaging	De-escalate follow-up
Indeterminate	Low-level Tg or nonspecific imaging	Observe, repeat testing
Biochemical incomplete	Elevated Tg, negative imaging	Intensify monitoring
Structural incomplete	Structural disease present	Treat (surgery/RAI/systemic)

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8) THE WHOLE THING IN ONE SENTENCE

Risk category → determines surgery extent → determines RAI need/dose → determines TSH suppression → determines follow-up intensity → determines need for systemic therapy if RAIR.

Sam Moslemi, MD